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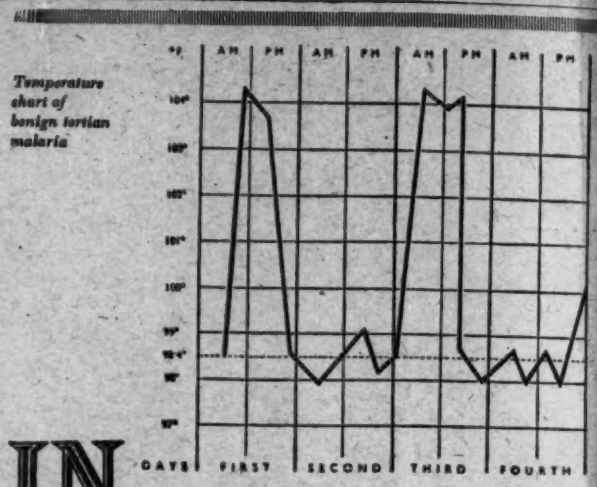

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 17 1949

THE RESULTS OF THYMECTOMY IN MYASTHENIA GRAVIS*

BY

GEOFFREY KEYNES, M.D., F.R.C.S.

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It is now eight years since the treatment of myasthenia gravis by thymectomy was first described by Blalock, of Baltimore, and seven and a half years since the first thymectomy for myasthenia was performed in this country. The experiment was initiated by Dr. Arnold Carmichael and his former assistant, Dr. James Carson, and I am proud to say that it was to my hands that they entrusted the performance of the first operation. This was at New End Hospital, in association with Mr. J. E. Piercy, in February, 1942, and the experiment has flourished to such an extent that we have now operated on 155 myasthenic patients, and a considerable number of operations have also been done by other surgeons in this country. It may be admitted, therefore, that enough patients have been treated and a long enough time has elapsed for it to be possible to survey the results in such a way as to form a true idea of the value of the operation, both in its immediate and in its remote effects.

A difficulty in the way of assessment of results is immediately encountered in the well-known tendency of myasthenia gravis to show "spontaneous remissions" of symptoms, for it may be said (and it has been said on several occasions) that the effect of operation, if it seems to be beneficial, may be really no different from what might have occurred spontaneously. It is necessary, therefore, to show that post-operative remissions are both more frequent and more prolonged than could have been expected in the course of nature. It will not, I think, be very hard to do this. First, we must get some idea of the remission pattern in a series of patients who have not had surgical treatment, and here we find help in a paper published last year by Professor A. M. Harvey (1948), of Johns Hopkins University.

He first reviewed a series of 87 patients published by Kennedy and Moersch in 1937. Twenty-seven of these patients had complete remissions, ranging from one month to 16 years; but the majority lasted less than one year, and the average was only 2.2 years. Some of these supposed "complete" remissions were probably, in fact, only partial. Of Professor Harvey's own series of 125 patients, 17 had significant clinical remissions, nine of which lasted over two years. Only one lasted over five years. Professor Harvey has noticed that since the introduction of neostigmine ("prostigmin") therapy spontaneous remissions have been less enduring, and that only one patient so treated had a remission of over two years. This observation is important, because practically all the patients in our series had had neostigmine therapy before operation, and if Professor Harvey is right an insignificant proportion of them would have had lasting remissions. Clearly it would be absurd nowadays to withhold neostigmine therapy on the chance of a few patients having spontaneous remissions. All, or practically all, will have had neostigmine, and the probable incidence of spontaneous remission lasting more than two years would be extremely small.

Four Categories of Results

I have referred on other occasions to the difficulty of assessing results in a disease so extraordinarily variable as myasthenia gravis. In my first communication (Keynes, 1946a) the patients were divided into the four following categories according to results, and the same method is still adopted: (A) Quite well; no symptoms; no neostigmine. (B) Virtually well; minimal symptoms; small dose of neostigmine. (C) Some improvement, often considerable; neostigmine still necessary. (D) No change.

Before considering the numbers that we have placed in these four categories it is necessary to emphasize that those patients who have been found to have thymic tumours have been excluded. The course of the disease and the effect of operation in these patients have been so different from the others that we believe a truer view of the value of operation can be obtained if we first consider only those who were free of tumour formation. Tumours can now nearly always be diagnosed by radiology before operation is undertaken, so that these patients can be set aside for a different plan of action; they therefore form a group for separate study. The incidence of tumours has been found to be 11.6% of all patients, so that the number of patients remaining for assessment is still satisfactory after this deduction has been made.

Patients have been carefully followed up, a few necessarily only by post, since they live in distant parts of the country or in the Dominions. The great majority have been seen personally, and not only by me and by my surgical colleague, Mr. J. E. Piercy. Patients at Queen Square have been seen by Dr. Carmichael and other members of the staff; those at New End by Dr. Raymond Greene; and those at St. Bartholomew's by Dr. Aldren Turner and Dr. Scowen. The number of patients treated privately has been insignificant.

The number of patients available for assessment, after deducting the post-operative deaths (10), the tumours (18), and the few that have not yet been assessed (7), is 120.

The figures for the four categories described I find to be as follows:

(A) 39 (32.5%)	(B) 40 (33.3%)
(C) 31 (25.8%)	(D) 10 (8.3%)

*A lecture given at the National Hospital for Nervous Diseases, Queen Square, on July 7.

Operative Mortality

The results of the operation can naturally be assessed only among those who have survived the operation—though death is unfortunately one of the possible results, and this must be carefully considered. The total number of patients who died as the immediate result of the operation is 10, but a high proportion of these deaths occurred during the early stages of the experiment, when experience of the operative technique and of the management of patients was small. This is reflected in the fact that five deaths occurred among the first 18 patients and only five in the next 119 operations. If it is fair to take this long consecutive series as the basis, then 4.2% represents the present operative mortality in experienced hands. This is a low figure considering the relatively poor human material with which we have to deal, for myasthenic patients with their narrow margin of respiratory efficiency are unfavourable risks.

The cause of death may be attributed in almost all instances to pulmonary complications; in none, so far, to loss of blood at the operation or afterwards. The pulmonary complications have been occasionally those of an acute myasthenic crisis in which the patients drown in their own secretions; more often they have been attributable to atelectasis of part of a lung or to a flare-up of a pre-existing bronchitis. The risk is always greater in the older patients and in those with coexisting disease—and it is of course the older patients who tend to have the coexisting disease. Thus our death roll included a man of 37 with chronic alcoholism, a woman of 46 with rheumatoid arthritis and cardiac degeneration, and a man of 47 with thyrotoxicosis and cardiac degeneration. Whenever a pulmonary infection becomes established a vicious circle tends to follow, since any acute infection in a myasthenic patient tends to make the myasthenia worse and the response to neostigmine less complete.

Moreover, in the early part of the series we were learning, through experience that was sometimes bitter, how best to perform the operation and how to steer a myasthenic patient through the post-operative period. Before February, 1942, no one in this country had ever performed a total extirpation of the thymus gland. Knowledge of its anatomy was hazy, and some of the information regarding its natural history was erroneous. Blalock's first communication gave very little technical help, though it emphasized the necessity for giving the patients an intravenous drip after operation.

Improvement in Technique

I am not now concerned with details of technique, but naturally our handling of the thymus did improve with experience, and soon it became obvious to us that the prime necessity was to keep the patients dry. To give an intravenous drip to a patient who had not lost a great deal of blood, and who did not suffer from much surgical shock, was unnecessary, and in a patient who tended anyway to produce an excessive bronchial secretion it was actually pernicious. As technique improved we realized the importance of removing the thymus without injury to the pleura, since even temporary collapse of a lung is harmful to a myasthenic patient; also it is easier to ensure pulmonary efficiency if the pleura has not been opened than after any transpleural operation or after accidental opening of the pleura, which may be difficult to close. Nevertheless we still have occasional arguments with thoracic surgeons, who are so accustomed to transpleural operations in non-myasthenic patients that they do not yet appreciate the extra dangers introduced by the presence of myasthenia.

Another strange fact that not all physicians seem to know is that it is dangerous to give a myasthenic patient an enema. Almost invariably the patient will collapse with syncope. This sounds improbable, but we do not doubt that it is a real danger. Early experience on several occasions had warned us, but we had not seen it happen for a long time and had almost come to disbelieve it. We tried to ensure, however, that the ward sisters had fully warned everyone concerned. On one occasion recently the warning, though given in writing, had failed to register. An enema was given, and the patient became unconscious and pulseless. We hope that the experiment will never need to be repeated.

I have referred already to the myasthenic crisis characterized by excessive bronchial secretion, sometimes followed by pulmonary consolidation and death. Occasionally death may be due to a more suddenly fatal cause—complete failure of both heart and respiration.

In April, 1948, a girl aged 16 had travelled from Singapore to London for thymectomy to be performed. Six months previously she had developed symptoms of myasthenia, first noticed as weakness of the arms when brushing her hair. Later the symptoms were mainly bulbar, but varied greatly in severity from time to time. On the voyage to England she had several attacks of dyspnoea, which greatly alarmed her. An operation done in July, 1948, was no more than a skin incision and exploration with a finger in the mediastinum, because at this stage the presence of a tumour was suspected, and the incision was closed. She was then given a course of deep *x*-ray therapy to the thymic area. This had to be stopped halfway through because she became much worse, but it was afterwards completed, and ultimately she greatly improved. She increased in weight and became transformed in appearance, so that the next operation was undertaken with great hopes in December, 1948. A somewhat shrunken thymus not showing any obvious tumour was removed without difficulty and the girl was not immediately affected by the operation. Within two hours, however, there was a sudden failure of peripheral circulation, with extreme pallor. Respiration then ceased and she died in the course of a few minutes. Those who were watching her said that the respiration seemed to stop an appreciable time before the heart had quite failed. At the post-mortem examination no adequate cause for her death could be discovered, and it could only be assumed that this was a form of myasthenic crisis following the disturbance of the operation.

This has been the only instance of death taking place so soon after the operation, and this kind of reaction is clearly exceptional.

The First Patients

Having these facts on the debit side of the account, let me now turn to the pleasanter side and give some account of the post-operative course of the patients who survived. First things come first, and so I must describe the first patient on whom we operated.

This patient was a woman aged 31 who had had symptoms of myasthenia for between three and four years. In February, 1942, she was a patient in the National Hospital, Queen Square, and her symptoms were very severe. Also they were getting worse, together with some mild signs of thyrotoxicosis, and it was thought that her prospects of survival were extremely bad. Thymectomy was therefore suggested, and this was done on February 10, 1942, together with a partial thyroidectomy. Her post-operative course was stormy, though on the fifth day she noticed improvement in nearly all her symptoms, and diplopia, present for several years, had disappeared. Nevertheless this same day she had a severe attack of dyspnoea with much mucus, and almost died. Ten days later she was almost completely well, and neostigmine was reduced to one tablet four-hourly with ephedrine. She had some temporary setbacks after this, but soon returned to her occupation as a land-worker, and has remained well to the present time—that is, for seven and a half years.

The second patient in the series had a thymic tumour and succumbed to the operation.

The third patient was one of the worst with whom we have ever had to deal. He was a man aged 34 who had worked in the National Fire Service. Symptoms of myasthenia had started nine months before we saw him, and had rapidly become worse until he was practically helpless, even with large doses of neostigmine. In addition he had a severe thyrotoxicosis with paroxysmal fibrillation. He was clearly going to die quite soon unless something could be done, and we judged that it would be best to deal with the thyroid gland first. A subtotal thyroidectomy was done on May 2, 1942, and his condition was critical for a few days, with rapid auricular fibrillation. However, he recovered, and after a month's interval a thymectomy was undertaken. He now had no symptoms of hyperthyroidism, but his myasthenia was worse, and he was extremely weak. The operation was done on June 15, 1942, and he stood it well. Some of his symptoms, such as those affecting the voice and swallowing, improved rapidly. The recovery of his skeletal muscles was slow, the delay being partly due to pronounced wasting of the muscles of his thighs and shoulder girdle. He was still taking a small dose of neostigmine two years later, but eventually was able to leave it off entirely, and for the last four years he has been quite well. It is now seven years since the thymectomy was done.

The next patient was a woman aged 44 with a six-years history of myasthenia. A thymectomy was done in May, 1942, and there was great improvement at first. Later she relapsed, and four years after the operation was much the same as before it was done. She died in 1947.

The fifth patient was a sailor aged 22 who had had symptoms of myasthenia for only 11 months, but he was already very ill, and without neostigmine was almost helpless. A thymectomy was done in May, 1942, and during the first 14 days he rapidly improved. A relapse then occurred due to an acute mediastinitis, probably following the liberal scattering of sulphanilamide powder in the mediastinum before it was closed (this was never repeated). Four weeks later he was without symptoms, and neostigmine was no longer given. Since that time he has been quite well.

It therefore seems that three of the first four patients who survived operation have had complete and permanent remissions if upwards of seven years is to be regarded as permanent. The evidence already given regarding the incidence of spontaneous remissions seems to make it unlikely that these recoveries were unconnected with the operation.

The Clinical Picture

Knowledge concerning the function of the thymus gland, whether normal or abnormal, is still very imperfect. We suppose that in removing the thymus we are getting rid of the source of a " curare-like substance " which is discharged into the circulation, though the final proof of this is still lacking. The histology of the gland in myasthenia shows that it is undoubtedly abnormal, and before long we hope to have some light upon the biochemistry of the disease ; but even then we are unlikely to know why it is that results of thymectomy are so erratic. This uncertainty has discouraged some operators, including even Blalock himself, from advocating surgery. But the manifestations of the disease itself are just as erratic as the results of surgery, if not more so.

The clinical picture is never exactly the same in any two patients. There are great variations in the muscles affected and so in the mode of onset and in the course of the disease. It may first be noticed in the ocular muscles as diplopia—suddenly appreciated, for instance, during a game of tennis ; in the levator muscles as ptosis ; in the facial muscles, first noticed when applying lipstick ; as difficulty in swallowing ; or as weakness in the arms or legs. The disease may advance rapidly or slowly, or it may be stationary for long periods. It may develop in a series of relapses, each being somewhat worse than the preceding one. This highly irregular pattern in the natural history of the disease is reflected in the effect of operation, but, provided that the results, taken broadly, are satisfactory, that is no reason for withholding operation.

Sometimes the effect of the operation is appreciated by the patient with an astonishing promptitude. I have known diplopia, present for years, disappear within 24 hours, never to return. Dysphagia is often abolished within a few days. Often within the first week the patient is aware of a new feeling of vigour in the limbs. The order in which symptoms disappear does not, however, obey any sort of rule. If generalizations are to be made, it may be said that ptosis and ocular palsies are usually the slowest features to disappear ; sometimes ocular muscles remain permanently paralysed when all other symptoms have gone, and are then unaffected by neostigmine.

A patient who showed this in an extreme degree was a woman aged 24. She had a 19-months history of fairly severe generalized myasthenia with pronounced ptosis. A thymectomy was done in June, 1945. She made a good recovery except that the ptosis remained, and she afterwards went with her husband to Czechoslovakia. In 1947 she returned to England because, although neostigmine seemed to have some effect on the ptosis, she was unable to obtain the drug. When examined she had no symptoms of myasthenia except the ptosis, and neostigmine had little or no effect on this. She was accordingly given splints for her eyelids, and advised that she no longer needed neostigmine.

Although the ptosis is sometimes persistent, the other facial muscles usually recover well after operation.

In May, 1948, a patient from Australia who was in St. Bartholomew's Hospital gained widespread notoriety in the press as " the girl with the frozen smile." She was a girl aged 16½ with an eight-months history of severe generalized myasthenia showing complete immobility of the facial muscles. Her recovery after thymectomy was almost complete. She still takes a small dose of neostigmine, but her smile has been unfrozen, and this change took place within a fortnight of the operation.

Among those who have undergone complete recovery are a few individuals who are unable, for psychological reasons, entirely to give up taking neostigmine. Their dependence on the drug has over months or years induced a state of mind in which independence of it seems too good to be true, and they still believe it is necessary to take a tablet at irregular intervals, particularly in the evening, when normal fatigue is felt. The most extreme example of this was a girl who would take a tablet on Saturday evenings but at no other time. On inquiry it was found that this was preparatory to going to a dance. Examination of these people will not detect any signs of myasthenia.

It has been suggested by Professor Harvey (1948) that the administration of neostigmine might interfere with the effect of operation in the same way as it appeared to do with the occurrence of spontaneous remissions. In this connexion the following history is of interest.

A woman aged 37 was operated on in September, 1943. She had been the first patient to be treated in this country with neostigmine. She had had symptoms of myasthenia for 17 years, and had received neostigmine therapy for nine years. Though certainly better than before, she has not experienced very great benefit, and now, nearly six years later, she is still in category C.

Nevertheless a general survey of the results with special reference to the period of neostigmine therapy did not reveal any constant relation between them, and there is no justification for basing a prognosis on this evidence.

Failures

It will have been noticed that a small proportion of patients have not undergone any improvement at all. They have not necessarily been those who had severe symptoms of the disease or a long history.

A doctor aged 56 had mild myasthenia for one year, mainly affecting the movements of the lower jaw and lips. The thymus when removed in February, 1946, was quite large, though rather fatty in consistency. The patient's immediate response to the operation was excellent, and he left hospital a fortnight later without any symptoms of myasthenia. Nevertheless a month later he had relapsed to the same myasthenic level as before operation, and there he has remained ever since. He takes 45 mg. of neostigmine daily, with good response.

Another patient who failed to improve after a short history of disease was a man aged 47 who had myasthenic symptoms for two years, especially affecting the ocular muscles. His response to neostigmine was slow. After thymectomy, done in July, 1946, he improved a good deal and was able to return to work in a shop; but 18 months after operation he had relapsed to the same state as before.

A third failure was observed in a woman, aged 26, with moderately severe myasthenia of 15 months' duration. Thymectomy was done in January, 1947, and up to the present time she has not improved at all.

Nevertheless the average age of the failures has been nearly 40, including patients of 39, 41, 47, 56, and 61 years. The youngest was 26. Their histories have also tended to be long, including ones of 5, 8, 12, 12, and 20 years. Since, however, there were four others of 3 months, 1 year, 1½ years, and 2 years, clearly no general inference can be drawn at present. The number is too small for an average length of history in this category to have much meaning.

Age of Patient and Duration of Disease

When we examine the ages of the patients in the other three categories we find that A and B have a considerable proportion of patients of the age of 20 or below, whereas in category C only three are under 20. If the average ages in these categories are calculated, however, the differences are inconsiderable: (A) 28.3 years, (B) 28.4 years, and (C) 32.1 years. It seems, therefore, that the influence of age on the results is less important than at first appeared probable. On the other hand, the calculation of the average duration of the disease is more illuminating: (A) 2 years 2 weeks, (B) 5 years 4½ months, and (C) 7 years 7 months. Here the differences are very striking, and it seems clear that a long history is prejudicial to recovery after operation.

This confirms what I have stated in a previous communication (Keynes, 1946b). It seemed that on the whole the best results were obtained in patients with short histories and the worst in those with long histories, though it was seen that there were exceptions in both directions. It still remains true that the quickest and most complete post-operative remissions are to be expected after short histories, but as time passes it becomes plain that many of the long-history patients will ultimately give unexpectedly good results, although it may take longer to achieve them.

In November, 1948, I operated on two women of this type. One, aged 48, had been bedridden for 12 years; the other, aged 37, had not moved except in a wheel-chair for 27 years. After operation both improved slowly over several months, and, though their remissions are far from complete, both are now able to walk.

Many other patients with histories of five years or over have continued to improve slowly and have been upgraded from category C to B, or even to A.

Another long-term patient was a man aged 38 who, when first seen, had not yet been diagnosed as myasthenic. His appearance, however, was typical, and a test injection of neostigmine, to his surprise, established the diagnosis. He then admitted that he had crept through life only with difficulty, and that his condition had been much the same ever since he could remember anything. He afterwards produced photographs of himself at the ages of 2 and 4½ years, from which it was evident that he had been myasthenic since infancy. His history therefore covered almost 38 years, and when he came under observation he was getting steadily worse, with generalized and bulbar symptoms. He eventually decided to submit to thymectomy in September, 1947, and since that time has steadily though slowly improved. Now, nearly two years after operation, he still needs a small amount of neostigmine, but has been assessed as B, being able to lead a normal life.

Myasthenia Gravis in Infants

The history of this patient introduces the subject of myasthenia gravis in infants, which has specially engaged my interest since I was repeatedly told that the disease was unknown in children. A photograph of the last patient described showed him as apparently suffering from myasthenia at the age of 2; but this did not surprise me, because two years previously I had been asked by Dr. Wyllie to see a patient at Great Ormond Street Hospital for Children.

She was a girl of 4½, who had been admitted apparently moribund, with acute respiratory distress and cyanosis. An experimental injection of neostigmine had an immediate result, and it was then realized that she was suffering from acute myasthenia, symptoms of which had been present for at least a year. I removed the thymus in November, 1945, and she made a good recovery. A year later she still had mild symptoms, but was able to lead a normal life and was described as tireless.

Two months after this incident, which was the first of its kind ever known at Great Ormond Street, a child of 2½ was admitted in a similar state. She was cyanosed and helpless, and again was immediately restored by neostigmine. I operated on this child in February, 1946, and removed what I thought was the whole of the thymus gland. She made a good recovery, but it was only temporary. Four months later she had a severe relapse and quickly died. At necropsy a thymus gland was found equal in size to the specimen I had removed. It was evident that I had removed only one lobe of the gland and had failed to find the other—the only occasion, so far as I know, on which this has happened.

I have not seen another myasthenic infant since this date, though Griffith (1949) described an undiagnosed example. This child had died with symptoms exactly resembling those of the Great Ormond Street children, and it is probable that in the past many children have died of myasthenia, the true diagnosis not having been suspected.

Selection of Patients

Whenever the results of any operative procedure are rather better than preconceived ideas will willingly allow, the charge is made that there has been "selection" of patients. The implication is that unfavourable ones have been eliminated, so that the results seem better than they should be. In the present investigation there has admittedly been some selection of patients, but this has not been exercised by ourselves. It has been through the physicians that most of the patients have, very properly, come to the surgeons, and it is they who have made the selection, which has therefore been in the direction of providing unfavourable rather than favourable material.

Physicians have naturally hesitated to submit to operation patients with only the milder manifestations of myasthenia, such as diplopia, and especially those whose symptoms did

not seem to be progressive. On the other hand, they have not hesitated to recommend operation for patients who were seriously disabled by the disease or whose symptoms were becoming progressively worse. On the surgical side very little selection has been exercised, though a very few patients have been rejected on the ground that operation would clearly be fatal. Sometimes patients have been kept under prolonged observation in order to seize the opportunity of operating when the disease was in a favourable phase.

A patient recently admitted to St. Bartholomew's Hospital under Dr. Scowen had been myasthenic for 16 years. There had been periods of remission, usually partial, but on the whole the disease was progressing, and during the last six years had been very bad indeed. It was found that she responded well to injections of neostigmine, and in six years had had 24,000 of these, many given by her husband, who, being by profession a reader of meters, was accustomed to keeping records. Often the patient herself was too weak to reach for the syringe. She spent two months in Dr. Scowen's ward, and underwent some improvement in this period. When the moment was deemed favourable, the operation was done. This was on June 29, 1949, and she is now improving, the daily dose of neostigmine having been reduced from 270 mg. before operation to 180 mg. at the present time.

Dr. Arnold Carmichael has been so impressed with the results of operation that we have operated at his request on one patient who had no symptoms of myasthenia at all. This is not so odd as it sounds.

The patient, a girl aged 14, had had several attacks of myasthenia, with brief complete remissions between attacks. But Dr. Carmichael was satisfied that each attack was proving a little worse than the one before, and therefore asked for the operation to be done at the safest time—that is, during a remission. This patient has now remained well for six months since the thymectomy was done.

We have operated on one other patient during a remission. This was an Irish youth of 21 who had lost all confidence in himself owing to his relapses, though they were mild. He had developed a myasthenic mentality, which prevented him from following any occupation whatever. Now, two years after thymectomy, he has admitted that he is perfectly well, and he started to work some time ago. Such is the power of surgery over a work-shy neurosis even in a myasthenic Irishman.

It is unnecessary to emphasize the importance of a careful follow-up of thymectomy patients, as this applies to most diseases; but it is worth noting that with the passage of time the results after this operation tend to encourage both surgeon and patients. Many of them undergo a slow improvement over a long period, and very few show the opposite tendency. More patients therefore gain promotion in the ABCD classification than have to be put back, so that each time I have published results they have shown slight improvement on the time before. It must be admitted, however, that there are a few qualifications to be made. Even after apparently complete recovery some of the female patients find that there is a perceptible relapse at the menstrual periods. Secondly, both sexes, although their vigour is normal for ordinary exertions, sometimes find their strength is not completely restored for sustained exertion. It may be, therefore, that the Saturday evening tablet is not entirely psychological in its effect. Thirdly, there seems to be in some patients an irreversible change in one or more ocular muscles and in the levator of the upper lid, the movements being unaffected either by operation or by neostigmine.

Side-issues

It will probably be expected of me to say something on an important side-issue—namely, the relation of myasthenia to thyrotoxicosis. Several writers have thought that there might be some such association, the belief being encouraged by the close anatomical and morphological relationship between the thyroid and the thymus, but we have not found any convincing evidence of this. Only four patients in the whole series of 155 have shown a definite thyroid excess, and in only one was it at all serious. Two of these patients I have already described. A third succumbed to the operation.

The fourth was a woman of 27 who was admitted to hospital with a diagnosis of thyrotoxicosis only, although soon after the onset of this in December, 1946, she had had occasional attacks of diplopia. Ptosis of the left eyelid followed, and then weakness of the left arm and both legs. The whole myasthenic picture then became more pronounced. Mr. J. E. Piercy performed first a subtotal thyroidectomy and then a total thymectomy. At the present time she is free of any symptoms of either disease on three or four tablets of neostigmine a day.

It has been pointed out by Dr. Raymond Greene (1949) that all the ocular muscles responded to neostigmine except the external recti, but that these steadily recovered after the thyroidectomy. The ocular movements therefore showed the mixed effect of myasthenic and thyrotoxic asthenia, each muscle responding to the appropriate treatment. Beyond this we have no evidence to offer. An incidence of four patients with thyrotoxicosis in 155 myasthenics does not seem to afford a basis for any conclusions, though it is perhaps somewhat higher than would be expected from mere probability.

Another side-issue which may be included among "results of operation" is the evidence concerning the supposed enlargement or persistence of the thymus gland in myasthenia. It has seemed to us that the size of the gland bears no relation to the severity or incidence of the disease. Apart from tumours the weight has varied from 3 to 36 g., the average being 15 g. It is now established that the thymus normally persists, and that it does not weigh more in myasthenic patients than in normal people of the same age, among whom the variation is just as wide. The only consistent abnormality has been in the microscopical appearance of the gland, as described by Bratton (1948) and Castleman and Norris (1949). This almost always shows conspicuous lymphoid "germinal centres"; these are not found in the thymus glands of other people.

Tumours of Thymus Gland

As I explained at the beginning, I have considered in the foregoing remarks only the results obtained in the treatment of patients who did not have thymic tumours. I do not now propose to deal in detail with those who had tumours, as they must be the subject of a separate study. It soon became obvious, however, that the presence of a tumour implied a very much worse prognosis. Patients with tumours usually have a short history and severe symptoms which respond slowly and imperfectly to neostigmine. The operation risk is increased by these features as well as by the greatly increased difficulty of removal. The immediate response to operation may be dramatic, but the patients tend to show after a short interval a serious relapse, and the symptoms become irreversible. They have usually soon died with respiratory failure. Primary operation has therefore been very unsuccessful in our hands. We now prefer to treat these patients with preliminary deep *x*-ray therapy, followed by extirpation of the thymus with the tumour if it is possible. A few patients treated in this way have given more encouraging results than those subjected to primary operation.

One patient who had a primary removal of a tumour in January, 1947, followed by deep *x*-ray therapy in June was slowly deteriorating, until Dr. Douglas McAlpine treated him with tetraethyl-pyrophosphate, since when he has steadily improved.

Conclusion

The treatment of myasthenia gravis by thymectomy has been called "empirical," and so it still is in the sense that there are a number of questions to be answered concerning the intimate details of the disease. The connexion between myasthenia and an abnormal thymus gland is now well established, but there is no clue to how or why the gland acquires its abnormal function. The chemistry of the secretion which is producing myasthenia is still quite unknown, and no active principle has yet been isolated.

Fundamental knowledge, such as the truth about the physiology of the neuromuscular junctions, is still lacking, so it is not surprising that understanding of abnormal functions is still defective. Surgery may help to provide an answer to these questions, which are far from being purely academic. In the meantime surgery, with the help of neostigmine, has undoubtedly made a practical advance in being able to alleviate the lot of many of the unfortunate sufferers from myasthenia gravis. There are few more pathetic sights than an otherwise perfectly healthy girl or youth reduced to a state of dependence and physical helplessness, and few more gratifying sights than their dramatic restoration to normal activity, a feat which surgery can now on many occasions claim to have achieved.

Summary

From February, 1942, to July, 1949, 155 patients with myasthenia gravis have been treated by surgical extirpation of the thymus gland.

Of 120 patients who did not have thymic tumours and survived the operation, 79 (65%) have shown a complete or almost complete remission of the symptoms. These could not be accounted for as "spontaneous remissions."

The operative mortality in our hands is at present 4.2%.

The results are influenced by the duration of the disease before operation: the shorter the history the better the results.

Early operation is indicated by the above fact, and by the 11.6% incidence of tumours, the development of which should, if possible, be anticipated.

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A statistical study by V. A. Fenger and J. Nielsen[1] shows that in the period 1908–15 the average duration of life of a Danish doctor aged 25 was 3 years shorter than that of his opposite number in the general population. In more recent years this difference has diminished considerably. This study, brought up to 1944, shows that the mortality among Danish doctors is lower than that among the whole population with regard to tuberculosis, cancer, and accidents. But it is higher with regard to suicides, and more than 40% higher with regard to heart disease. A comparison is made with the studies of Dublin and Spiegelman in the U.S.A., and a table is drawn up by the Danes showing how the Danish and American findings compare with each other in respect of each important cause of death.

[1] *Ugeskrift for Laeger*, June 30, 1949, p. 737.

INCIDENCE OF CROSS-INFECTION IN CHILDREN'S WARDS

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In 1945 the British Paediatric Association began to interest itself in the problem of cross-infection in children's wards in hospitals, and an *ad hoc* committee was set up to consider the matter. Its report was published in the *British Medical Journal* of May 4, 1946 (p. 673). During the committee's deliberations it became obvious that the views and experience of individual paediatricians differed widely. There was not only little information on the incidence of cross-infection but also little evidence of the effect of the common methods used to prevent or control it. The result was a report in very general terms "in the nature of a preliminary discussion," and the collection of evidence on the incidence of cross-infection and the evaluation of methods for its control were left for later investigation. This report is the result.

It is not easy to give an adequate definition of cross-infection in this context, but that suggested by the above-named committee was accepted and used—namely, "To denote any infection acquired by a patient in the hospital environment. Clinically, it is an infection arising during the course of another illness for which the patient was originally admitted to hospital, and may attack the respiratory tract, gastro-intestinal tract, wound, skin, or mucous membrane, or be manifested as one of the specific fevers." This definition places the final onus of diagnosis on the paediatrician, who may or may not have help from bacteriological investigation. This does leave room for a difference of personal opinion, but it was felt that experienced paediatricians would hold relatively uniform views, especially as nearly all those taking part in the investigation had preliminary discussions in committee with their colleagues.

The main objects of the inquiry were to determine: (1) the incidence of cross-infection in children's wards (nurseries for the newborn were excluded); (2) the effect of cross-infection on morbidity and mortality; (3) the part cross-infection played in increasing the length of stay in hospital; and (4) the methods used to prevent cross-infection and their relative efficiency.

Information Sought

Fourteen hospitals were selected as representing a cross-section of children's wards in which patients were under the clinical charge of an experienced paediatrician. The hospitals included examples of children's wards in a general hospital, wards in hospitals for children only, wards in teaching and non-teaching hospitals, and wards taking long-stay cases. In all, the records of 26 different wards were utilized.

Special cards were prepared and issued to each ward for recording the information in respect of every patient admitted. These asked for details of the age, sex, diagnosis on admission, how the child was disposed in the ward on admission and during its stay (e.g., bed in open ward, cubicle), and method of dispersal (e.g., transfer to another ward, transfer to isolation hospital, home). If cross-infection took place its date was to be noted, together with

the suspected source of infection and any relevant bacteriological investigation. Any increased length of stay in the ward as the result of cross-infection was to be estimated, and a special comment was asked for if it was felt that the death of a patient was in any way attributable, either partly or wholly, to cross-infection. The types of cross-infection were divided broadly into: acute specific fevers, upper respiratory infections, lower respiratory infections, gastro-enteritis, and other infections.

A record card was filled in for each child on admission and observations made during the children's stay were dated as at noon of each day. In this way 9,619 cases were covered in the survey. Records were kept from March 1, 1946, to February 28, 1947, but, for reasons to be explained later, analysis was made for only 11 months—i.e., from April 1, 1946, to February 28, 1947.

In addition to the individual patient's record each ward unit was supplied with a questionary form. This asked for information on the following:

Official number of cots in ward.
Upper and lower age limit of children admitted.
Type of case admitted (e.g., medical, surgical, tonsillectomy, skins).
Ward design.—Open ward; length, breadth, height, and distance between cot centres. Number of cubicles, distinguishing single, double, and multiple, giving length, breadth, and height of each cubicle and stating whether it was open or closed.
Quality of ventilation in wards or cubicles.
Method (if any) of isolating new admissions.
Whether a special room is available for dressings.
Method of ward heating.
Number of sluices, lavatories, and wash-basins in each ward or cubicle.
Provision for bed-pan sterilization, napkin disposal, dressings disposal, and refrigerators.
Whether or not a special room and/or special staff is available for preparing feeds.
Method of ward-cleaning—dry sweeping, wet or oiled sweeping, oiled floors, oiled blankets, vacuum-cleaning.
Method of air sterilization (if any).
Status and qualification of staff: ward sister, number of trained nurses, number of student nurses.
Number of nurses per ward—average and minimum per day and night.
Whether "runners" are employed at night.
Whether the nursing staff are immunized against (*a*) diphtheria, (*b*) other infections.
Number of maids per ward.
Whether masks are worn by nurses, doctors, students, and maids.
When masks are worn.
Whether visiting is allowed—how often, how long, how many per bed, and whether children visitors are excluded.
Whether acute fevers are transferred or nursed in the ward.
Any other relevant information.

Data Received

Of the total of 9,619 cases surveyed in the 11 months under review, 679 showed evidence of cross-infection during their hospital stay. This represents an overall incidence (irrespective of length of exposure in hospital) of 7.1%. The frequency of the individual types of infection is shown in Table I.

It is interesting to note that 92 of these children experienced at least two cross-infections and 20 at least three. Tabulation of the acute specific fevers by ward age showed that 23 of the 80 cases of measles were "acquired" before the 10th day, which means that the disease was in the incubation period when the child was admitted to hospital. Similarly three of the five cases of mumps developed before the 21st day in hospital, five of the 24 cases of whooping-cough developed before the 10th day, and three of the 20 cases of chicken-pox developed before the 14th day. It might be objected that these were not strictly examples of cross-infection and should therefore be excluded from analysis. The objection rests entirely on the interpretation of the word "acquired" in the definition of cross-infection; if these were to be excluded many other infections, both of the upper and of the lower respiratory tract, which were not traceable because the length of their incubation is not known would also have to be excluded. It may be added that admission during the incubation period of an infectious disease was in no way confined to one hospital. In point of fact it has been shown that the cross-infection rates at the individual ward ages would have been little affected if these cases had been omitted.

TABLE I

Type of Infection	Total No.	Percentage Distribution
Upper respiratory infections	*257*	*37·8*
Acute specific fevers	*155*	*22·8*
Measles	80	11·8
Whooping-cough	24	3·5
Chicken-pox	20	2·9
Scarlet fever	14	2·1
Dysentery	11	1·6
Mumps	5	0·7
Diphtheria	1	0·1
Gastro-enteritis	*141*	*20·8*
Lower respiratory infections	*57*	*8·4*
Other infections	*69*	*10·2*
Total	679	

This evidence strengthens the view expressed in the previous report that an essential barrier to cross-infection is a senior medical officer who shall be responsible for all admissions to the ward.

Effects of Cross-infection

On the record card of each patient an estimate was given of the increased length of stay in the ward attributed to cross-infection. No additional stay was occasioned to 65%, up to an additional week was necessary for 17%, up to two weeks for 14%, and up to three or more weeks for 3.6%. The average additional length of stay in the whole series was 4.59 days, and for those 225 children who did have to stay longer their average increased stay was 12 days. This is an important economic aspect of the problem, for in addition to the increased bed occupation in the original hospital there must be added the days spent in an isolation hospital, home, or other institution. This increased occupancy of beds is a strong argument which may be used in favour of administrative or structural measures that may be adopted to lessen cross-infection, as any means which will reduce the length of hospital stay will therefore increase the total annual occupancy of the beds.

Hospital infection may not only increase the length of a child's illness but contribute materially to a fatal issue. We all know of the patient with pyloric stenosis who is successfully operated upon but who dies later from a gastro-enteritis developed whilst in the ward recovering from the operation. Information was sought by the specific question, "Did the observer consider death was attributable in part or whole to cross-infection?" The answer was in the affirmative in 41 of the 50 deaths which occurred in children developing an infection while in hospital (death wholly attributable to cross-infection, 13; death partly attributable to cross-infection, 28), so that of 587 patients who incurred an infection in hospital 7% died wholly or partly because of that infection. As illustrative of deaths wholly due to cross-infection may be cited two patients admitted for

repair of hare-lip, both of whom died of gastro-enteritis. The infections in this group were as follows:

Gastro-enteritis	17 cases (1 Sonne, 1 Flexner Z)
Pneumonia	16 „
Pneumonia and enteritis	2 „
Upper respiratory infection	2 „
Measles	1 case
Meningitis	1 „
Staphylococcal pyaemia	1 „
Stomatitis	1 „
Total:	41 cases

Only seven of these children were over 2 years old, and of the remaining 34 cases no fewer than 24 occurred in babies under 3 months old, thus illustrating the dangers of hospitalization to small babies.

Statistical Problems

The main statistical problems presented were (*a*) to calculate an index suitable for comparing the incidence of cross-infection in the various hospitals and wards; (*b*) to select a suitable standard of comparison; and (*c*) assuming that the incidence would be found to vary between the wards, to determine whether the rates showed any association with the architectural and administrative factors of the ward. One inherent deficiency in the data was that only infections which became manifest during the patient's stay in hospital were recorded. No provision had been made for following patients up, with the result that the number of cross-infections which occurred in hospital but which developed after discharge was unknown, and the value of the inquiry is lessened to that extent. This once again stresses the advisability of giving careful consideration to the statistical aspects when investigations of this nature are in their initial stage.

No index of cross-infection would be adequate which failed to take into account the differing lengths of time each child was exposed to risk—i.e., the duration of stay in hospital. From the information provided the numbers of patients exposed to risk of infection in each ward at each ward-age (i.e., age 1=1 day after entry, age 2=2 days after entry, etc.) were obtained. The numbers of cases occurring in each ward were also tabulated, and by relating the total number of cross-infections which occurred at each age in all the wards combined to the aggregate exposures at the relative ages a cross-infection rate at each ward-age for the aggregate of all wards was obtained. These are the standard rates. In calculating them one difficulty which must be recounted necessitated a change in the initial date of the experience. All children admitted for treatment during the period of the survey are admitted at ward-age 0, but the investigation also covered patients who were in hospital when the inquiry started. To overcome this difficulty it was decided that the experiences should begin on April 1, 1946, instead of March 1. This reduced the length of the inquiry to 11 months, but from the March records the length of stay in hospital previous to April 1 could then be calculated for the majority of children who were in hospital on that day.

The smoothed values of these standard rates (Table II) show that the rate of cross-infection in all hospitals combined rose from 3 per 1,000 in the first four days after entry to 4.9 per 1,000 patients who were in the wards on the 20th–24th days, fell to 3.5 per 1,000 for days 55–59, and was as high as 6.8 per 1,000 for those exposed to risk in days 85–89.

TABLE II.—*Cross-infection Rates (smoothed*) per 1,000 Child-days Exposure (5-day groups); All Wards Combined; Both Sexes. Limited to 91 Days After Admission to Hospital.*

Ward Age Groups	Cross-Infection Rate per 1,000 Exposures	Child-days Exposure in Each 5-day Group
0–	2·96	37,306
5–	3·88	30,065
10–	4·47	20,106
15–	4·79	13,981
20–	4·89	10,655
25–	4·81	8,341
30–	4·61	6,641
35–	4·33	5,355
40–	4·03	4,377
45–	3·75	3,560
50–	3·55	3,030
55–	3·48	2,611
60–	3·58	2,274
65–	3·91	2,056
70–	4·52	1,815
75–	5·46	1,568
80+	6·77	1,383

* $y = 2{\cdot}358 + 0{\cdot}259x - 0{\cdot}00801x^2 + 0{\cdot}0000669x^3$
where y = cross-infection rate, x = ward-age in days.

Standard Cross-infection Ratio

For each ward the number of patients exposed to risk at days 0, 1, 2, 3, 4, etc., was known and the number of cross-infections which would have been expected amongst the numbers exposed to risk at each ward-age if the standard rates (all wards combined) had been effective could be calculated for each ward:

$$\frac{\text{Exposed} \times \text{standard cross-infection rate}}{1{,}000}$$

The numbers expected at each age, aggregated to 91 days or 183 days or 365 days, gave the total number of cross-infections expected in every ward for the respective periods at the standard rates. The number of infections which actually occurred expressed as a percentage of the number expected in the same period provided a comparable index of cross-infection for the different wards. If the actual number was in accordance with expectation the ratio would of course be 100. This index has been termed the "Standard Cross-infection Ratio," because the method of its construction is the same as that of the standardized mortality ratio used by the Registrar-General for comparison of the mortality experienced in different occupations.

When the wards investigated are arranged in order according to the magnitude of the standard cross-infection ratio they may be divided into three groups: those with a high incidence, in which the ratio lies between 140 and 350; those with a moderate incidence of between 60 and 140; and those with a low incidence, below 60, even dropping as low as 29 for a stay of up to 91 days. There are nine wards in the group with a high incidence, eight wards in the moderate group, and nine in the low-incidence group (Table III). It is interesting to observe the extreme

TABLE III.—*Wards Arranged in Order According to the Magnitude of the Standard Cross-infection Ratio, Forming Three Groups with High, Moderate, and Low Incidence*

S.C.R.	Ward	Stay Up to 91 Days
High (140 or over)	Hospital A, Ward 1	350
	„ B, „ 1 (infants)	205
	„ C, „ 1 (medical, babies)	190
	„ D, „ 1 (infants)	188
	„ E, „ 1 (convalescent)	185
	„ F, „ 1	148
	„ G, „ 2	146
	„ H, „ 1	145
	„ C, „ 1	140
	„ I, „ 3 (surgical, babies)	133
	„ C, „ 1	123
	„ E, „ 4	111
Moderate (60–140)	„ J, „ 2 (convalescent)	90
	„ E, „ 1	88
	„ K, „ 3 (convalescent)	84
	„ L, „ 1 (infants)	73
	„ A, „ 1	72
	„ M, „ 2	58
	„ K, „ 1	56
	„ B, „ 2	55
	„ G, „ 2	49
	„ L, „ 2	47
	„ L, „ 2	38
	„ D, „ 3	34
	„ N, „ 2	33
Low (60 or under)	„	29

variation in the wards, all of which were under the supervision of expert paediatricians. To note a specific example, one hospital which is modern and with isolation facilities has a high cross-infection rate in its babies' ward but a low one in its older children's ward, both wards being identical in design. The paediatric supervision, both senior and registrar, is the same for both wards, the recording of cross-infections was done by the same individual, and the nursing staff was drawn from the same training school. It is interesting to note that no fewer than four different hospitals are represented in both the high and the low group.

The amount of material for survey was inadequate for calculation of standard cross-infection ratios based entirely on patients who on admission were under 1 year old, 1 to 4 years, 5 to 9 years, and so on. All that was possible was to distinguish 10 wards which excluded entirely children under 1 year of age. Table IV compares the standard cross-infection ratio of those wards with that of wards to which infants were admitted.

TABLE IV

Type of Ward	S.C.R.			
	Low	Moderate	High	Total
Wards excluding infants under 1 year ..	6	3	1	10
Wards admitting infants	3	5	8	16
Total	9	8	9	26

A statistical test showed significant association between the standard cross-infection ratio ($\chi^2=5.8$: $P<0.05$) and the admission of children under 1 year of age. This increased danger in infancy is a fact well known to all practising paediatricians.

This relation between age and cross-infection is the only "statistically significant" result of our attempt to correlate incidence with environmental influences. Other factors which were statistically investigated but gave no conclusive results were: type of case admitted (surgical, medical, etc.); relation between standard cross-infection ratio and architectural features of cubicles; average square feet per cot; quality of ventilation; employment of "runners"; method of ward-cleaning; and patients' visitors and frequency of visiting-days. (Because of their negative findings these analyses are not recorded in full.) The unit for these analyses was the ward, and with only 26 units it was hardly to be expected that many significant relationships would appear.

The difference between the wards with regard to cross-infection remains difficult to explain fully. There is no doubt that imponderables must play an important part—namely, the quality of the medical and, particularly in this problem, the nursing care. We have noticed that there has been an increase in infection when there has been a change of nursing staff, though we have no figures to support this, and it would seem that there is still a tendency to under-staff babies' wards at night. Thus all the careful work done by the day staff can be undone through a shortage of nurses at night to do the common tasks with adequate care and time.

Another factor which is difficult to assess is the question of immunity of a child admitted to a strange bacterial or viral environment. Bacteriological studies were not undertaken in this review except in a few instances, for in one of the commonest of the infections, gastro-enteritis, there is no specific organism to act as an indicator. It is well known that babies are slow in acquiring an immunity reaction, and this may well be a factor in the increased infection found in the very young.

Conclusion

On the whole we feel that this inquiry, which entailed a great deal of work for many people, has been disappointing in that it has not resulted in our being able to give advice to hospital planners on the value of the common architectural practices in preventing cross-infection. Further inquiry on these matters which will stand up to statistical scrutiny is desirable. We feel, however, that we have at least obtained some figures that are of interest if only in showing for the first time the extent of cross-infection in a sample of hospital wards in this country and in drawing attention not only to its prevalence but also to its dangers.

It should be recalled that the wards chosen were all under expert paediatric supervision and therefore the number of cross-infections was, or should have been, minimal. However, the very fact of the inquiry taking place in a ward helped to draw attention to the condition and so in itself may have reduced the incidence a little. If, then, hospitals of this status have a cross-infection rate as high as 7% it may be suspected that other hospitals with less facilities and less expert staff have a higher rate.

In this respect it has been interesting to note the reaction in some hospitals visited outside the scope of this inquiry to the question, "How much are you troubled by cross-infection?" In many instances the reply has been given that cross-infection has never occurred, from which it seems likely that the problem has not been acknowledged or recognized. If, then, this paper can do something to interest those responsible for the care of children in hospital in this aspect of their work we feel we may have accomplished something of value.

Summary

Records of all children admitted to hospital during the year March 1, 1946, to February 28, 1947, were provided by 26 children's wards in 14 hospitals in Great Britain. From these records information was obtained as follows: (*a*) The overall incidence of cross-infection in 9,619 admissions was 7.1%. (*b*) The average length of increased stay in hospital of these cases that developed a cross-infection was 12 days. (*c*) In 41 children death was attributable partly or wholly to cross-infection. (*d*) An index for the rate of cross-infection was calculated for each ward (standard cross-infection ratio) and was found to vary widely for the different wards even within the same hospital. (*e*) Attempts were made to correlate factors which might be related to the variations, which included ward architecture, equipment, nursing, staffing, visitors, type of case admitted, and the age of the children. The only "significant" finding was that cross-infection was commoner in wards which admitted infants.

The data on which this paper is based have been produced by the helpful co-operation of many sisters and registrars in the hospitals concerned and of the paediatricians who had the children under their care. The following hospital centres have contributed, and we are grateful to all who have helped: Belfast, Birmingham, Cardiff, Glasgow, Guy's, Great Ormond Street (including Tadworth), King's College, Leeds, Liverpool, Newcastle-upon-Tyne, St. Bartholomew's, and Warwick.

We wish to acknowledge many helpful suggestions made by Professor R. M. F. Picken during the course of the analysis. Our thanks are due to Miss Kathleen Davies and Miss Betty Goode, on whom has fallen the burden of the heavy tabulation and computing work, not all of which has been produced in this paper. We are also indebted to the members of the *ad hoc* Committee of the British Paediatric Association on Cross-infection for much valuable advice in the carrying out of this inquiry, and to the British Paediatric Association for a grant towards the computing expenses.

EFFECT OF TETRAETHYLAMMONIUM BROMIDE ON GASTRIC SECRETION AND MOTILITY

BY

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Tetraethylammonium bromide (T.E.A.B.) is known to produce a blockade of the autonomic nervous system, and has been used with this object in the investigation of peripheral vascular disease. The purpose of this paper is to examine its effects on the secretory and motor functions of the stomach.

Pharmacology

The site of action of tetra-alkyl-ammonium compounds is at the ganglionic synapses of the autonomic nervous system, where a blocking effect was first demonstrated by Marshall (1913). T.E.A.B. is a synthetic compound produced by the substitution of four ethyl groups in the ammonium radical of ammonium hydroxide. The chemical relationship of the drug to acetylcholine is:

T.E.A.B. Acetylcholine

The site of action of the two compounds is the same and is probably determined by their basic structural relationship; side-chain variants determine their pharmacologically different effects. The blocking effect of T.E.A.B. is probably due to the fact that the drug can replace acetylcholine in the neurohumoral chain at the autonomic synapse, thus excluding it. The transience of its action is probably also due to its similarity to acetylcholine, which is destroyed by cholinesterase.

The pharmacological effects are twofold. Sympathetic blockade leads to release of peripheral vasoconstrictor tone, a fall in blood pressure, and an increase in pulse rate. There is increased blood flow to the extremities, with increased skin temperature. Sweating is inhibited. Parasympathetic blockade leads to inhibition of gastric secretion and motility, inhibition of salivation, paralysis of accommodation, and transient impairment of the power to urinate or defaecate.

Side-effects are noted as follows. After moderate doses (less than 500 mg. intravenously or 20 mg. per kg. of body weight intramuscularly) there is a metallic taste in the mouth, with a sensation of warmth and flushing, transient peripheral numbness, light-headedness, loss of accommodation, and transient difficulty in urination or defaecation. After large doses ptosis, weakness, or even severe collapse may occur. While these severe manifestations are rare, the commoner side-effects make out-patient administration impracticable.

Effect of T.E.A.B. on Gastric Secretion

Published work on the effect of T.E.A.B. on gastric function comes mostly from America. Zweig *et al.* (1948) found that in normal subjects the gastric motility was completely inhibited for a total period of 45–100 minutes after intravenous injection. Unstimulated secretion was reduced by 85% and histamine-stimulated secretion by 70%; on the contrary, Neligh *et al.* (1947) noted no effect on histamine-stimulated secretion. Brown *et al.* (1948) demonstrated, in duodenal ulcer patients, inhibition of gastric motility and abolition of insulin-stimulated secretion. Ferrer (1948) reported effective reduction of excessive night secretion in patients with peptic ulcer.

1. *Studies by Alcohol Test Meals.*—We have studied the effect of T.E.A.B. on gastric secretion following an alcohol test meal in 20 cases (17 men and three women, eight of them suffering from duodenal ulcer). The method was as follows:

The patients were starved over nine hours, a Ryle's tube was passed at the end of this period and the fasting juice aspirated. Then 50 ml. of 7% alcohol was given and specimens were removed from the stomach every 15 minutes for one and a half hours and titrated. The following day, at the same hour, this procedure was repeated, but in addition 1 g. of T.E.A.B. was given intramuscularly as a 10% solution half an hour before the start of the test meal. The patients were interrogated regarding symptoms following T.E.A.B. administration. Blood-pressure readings were taken throughout. The average values for the 20 test meals are shown in Fig. 1. There is an average reduction of 5–10 clinical units of free HCl. Some reduction in the free HCl was noted in every case. In several the reduction was of the order of 20 units.

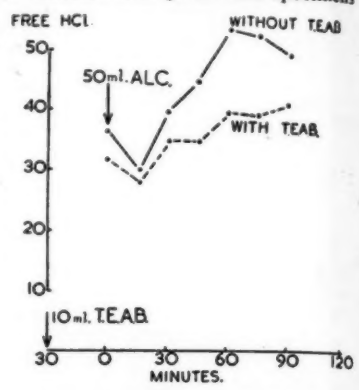

FIG. 1.—Effect of T.E.A.B. on gastric secretion after an alcohol test meal (20 cases, average values).

2. *Studies after Insulin Stimulation of Secretion.*—Because of the known pharmacological effect of T.E.A.B. in blocking vagus synapses it was of interest to investigate its action after the administration of insulin. In 1943 Hollander observed copious acid secretion in the gastric pouch of dogs in which he had induced hypoglycaemia; he found a pronounced acid secretion so long as the vagus supply to the stomach was intact and cessation on complete severance of all vagal fibres. This observation led to the development of the insulin test for vagus activity. It was employed as follows in our cases.

The alcohol test-meal technique already described was followed in 10 patients, with the modification that one and a half hours after the meal in each case 20 units of soluble insulin

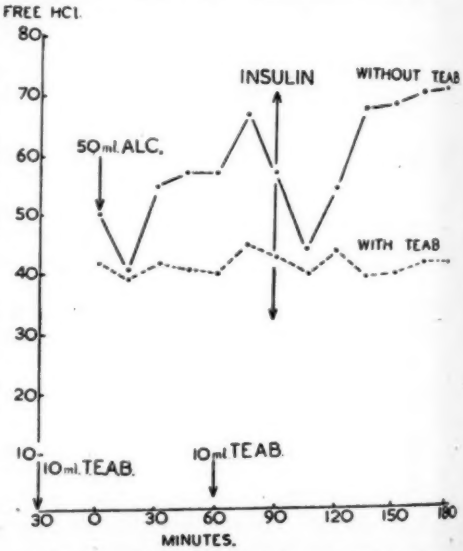

FIG. 2.—Effect of T.E.A.B. on gastric secretion after administration of insulin (10 cases, average values).

was given intramuscularly. A similar procedure was adopted in the same patients (on a subsequent occasion) after the administration of T.E.A.B. (The patients were all adults, eight males and two females, four of them suffering from duodenal ulcer.) The blood sugar in all cases fell below 55 mg. per 100 ml. The symptoms noted included weakness, hunger, and emptiness. The average of the 10 test meals is shown in Fig. 2. It will be seen that after T.E.A.B. the production of insulin hypoglycaemia failed to stimulate the secretion of gastric juice.

3. *Studies after Histamine Stimulation of Secretion.*—The response of the stomach to administration of histamine was studied by the method already described for insulin, an injection of 1 mg. of histamine being given at the end of 1½ hours in each case. In view of the effect of histamine on blood pressure no patient was used in this series whose blood pressure fell below 100 mm. Hg as a result of T.E.A.B. The average results of the 10 experiments (all adults — nine males, one female, including four cases of duodenal ulcer) are recorded over the entire three-hour period (Fig. 3). It will be seen that after T.E.A.B. the injection of histamine stimulated the secretion of gastric juice, but the response was not so great as in the control series.

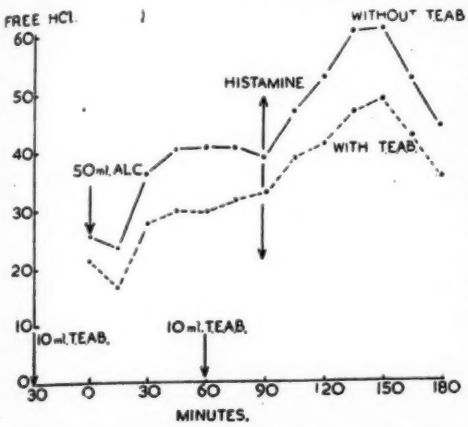

FIG. 3.—Effect of T.E.A.B. on gastric secretion after histamine stimulation (10 cases, average values).

4. *Studies on Spontaneous Night Secretion.*—Much attention has recently been devoted to the secretion of the stomach during interdigestive phases, and particularly at night. It is claimed that the nocturnal secretion is large in volume and highly acid, and that this unbuffered secretion expelled rapidly into the duodenum is of importance in the production of duodenal ulcer. Investigations of the action of T.E.A.B. upon the nocturnal secretion in 10 patients were made as follows.

The patients had nothing to eat or drink after 5 p.m. A duodenal tube with multiple perforations at its tip was passed at 8 p.m., the stomach emptied of its contents, and the secretion aspirated till 8 a.m. by means of constant suction set up by means of an electric pump. Narcotics were withheld. The following evening the experiment was repeated, giving 1 g. of T.E.A.B. four-hourly to a total of 3 g.

Night Secretion Tests (8 p.m.–8 a.m. Continuous Suction). Total Dosage = 3 g. of T.E.A.B.

Without T.E.A.B.			With T.E.A.B.			Average Reduction in Milli-equivalents/Hr.
Volume	Free HCl	Total Acid	Volume	Free HCl	Total Acid	
630	36	57	400	12·5	26·5	79%
105	12	22	55	0	6	100%
595	42	58	400	20	34	70%
750	56	66	305	33	46	76%
410	36	52	300	12	28	75%
640	9	19	274	9	30	60%
740	48	60	480	20	28	69%
1,170	28	34	372	15	33	84%
220	14	32	104	0	6	100%
692	13	22	165	4	24	91%

In 10 cases the volume of secretion was reduced, as was the acidity. The accompanying Table shows that T.E.A.B. brought about an average reduction of 309 ml. in the volume of the night secretion and a reduction of 80% in milli-equivalents per hour of the night secretion. All patients were cases of duodenal ulcer with severe symptoms. None complained of dyspepsia during the administration of T.E.A.B.

Effect of T.E.A.B. on Gastric Motor Functions

This was studied in five patients by means of gastrograms according to the technique described by Kay (1947). After a 12-hour fast the patients (all of whom were cases of duodenal ulcer proved later at operation) swallowed two Ryle tubes fastened together, one having an inflatable balloon attached at its tip.

The balloon was inflated to a standard pressure of 5–10 ml. of water and the column of air was connected to a tambour kymograph unit recording variations in intragastric pressure; the other Ryle tube may be used for aspiration of secretion or performance of the "water test" (Kay, 1947).

In normal individuals the gastrogram has four components (Johnson, 1948): (1) Postural tonus, characteristic of hollow viscera, fairly constant and independent of its degree of distension. (2) Tonus waves: these are regular gentle undulations of postural tone, which may be peristaltic in nature, with a frequency of three a minute. (3) True gastric contractions which are spastic contractions of the whole stomach, considerably increasing intragastric pressure. They are represented by sharp-topped waves lasting 30 seconds, and occur in normal individuals in bursts at intervals of 1½–2 hours with a frequency of 1–2 minutes. They are present in hunger pains and are greatly increased in amplitude and frequency in duodenal ulcer patients. (4) Cardio-respiratory effects: these are frequent small oscillations superimposed on the above intrinsic waves. They are due to respiratory movements of the diaphragm and cardiac pulsations; they occur with a frequency of 20 a minute. In five patients showing frequent true gastric contractions after a control period of 20 minutes, 1 g of T.E.A.B. was injected intramuscularly. After a latent period of 15–30 minutes tonus waves and true gastric contractions were abolished and postural tonus diminished: the effect persisted for 1–1½ hours, tonus waves returning before gastric contractions. There is a striking similarity between the gastrogram shown and that following vagotomy: in four of five patients this inhibition of vagal activity was found, the remaining case showing for 1½ hours diminished frequency, amplitude, and duration of contractions (Fig. 4).

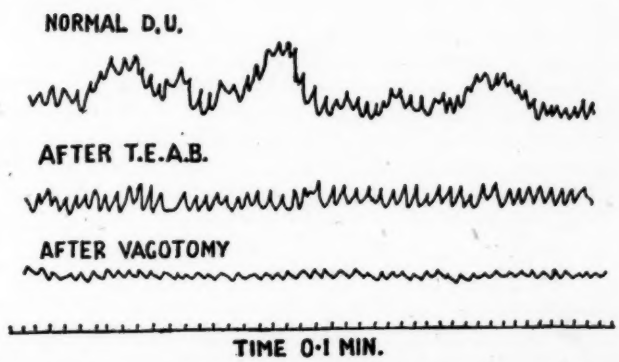

FIG. 4.—Gastrograms in normal duodenal ulcers, after injection of T.E.A.B., and after vagotomy.

Discussion

The administration of T.E.A.B. leads to a slight fall in gastric acidity as estimated by the alcohol test meal. After T.E.A.B. the induction of insulin hypoglycaemia fails to stimulate a rise in gastric acidity. This indicates the presence of vagal blockade and is in keeping with the known action of the drug. It can be assumed that such secretion as occurs after T.E.A.B. is due to the chemical mechanism of gastric secretion. It is interesting to note that after T.E.A.B. the injection of histamine does stimulate gastric secretion, albeit less than normally. This is interesting on account of the fact that histamine acts directly on the oxyntic cells, and so the reduction in acidity in this case cannot be due to an autonomic blockade. Hollander (1944) asserts that the oxyntic cells secrete acid of a constant strength; but if on histamine stimulation they secrete into a stomach which is comparatively amotile there will result a fair degree of buffering and dilution by alkaline and mucoid elements. This fall in acidity may therefore be attributed to retention, to which Johnson ascribes the same effect following vagotomy. He points out that in the amotile stomach there is difficulty in evacuating serial specimens completely, so that dilution of secretion occurs.

The reduction in night secretion is interesting. Because of the motility effect, it could be held that it was in part due to regurgitation of duodenal contents through a relaxed pylorus. A few experiments were abandoned because of bile-staining of the juices drained off; on the other hand, the 10 cases reported were free from bile in the suction specimen, and the volume in the 12-hour specimen after T.E.A.B. was less than that taken off the previous evening.

The average reduction in milli-equivalents per hour was 80%, comparing not unfavourably with 90% following anatomical section of the vagus.

The motility effect has been shown to be similar to that following vagotomy; but T.E.A.B., as well as inhibiting the parasympathetic supply of the stomach, might be expected to effect gastric function in some way by its action on the sympathetic. There are several records of the effect of splanchnic section on gastric secretion in man and animals. Brown (1933) could find no demonstrable change in free or combined acidity following complete removal of the sympathetic chain or coeliac ganglia in cats, and Ray (1942) investigated and found no change in gastric acidity after bilateral sympathectomy.

It has been claimed by Little *et al.* (1947) that T.E.A.B. is effective in preventing or modifying the course of peptic ulcer produced experimentally in animals. In view of its effects on the gastric secretion and motility, and particularly on the volume and acidity of the nocturnal juice, the hope was raised that it might be of value in the treatment of peptic ulcer in man. It is perhaps worthy of note that all 10 patients submitted to repeated injections of T.E.A.B. were free from pain during the progress of the experiment, whereas previously they had had incapacitating symptoms. T.E.A.B. has, however, certain practical disadvantages, especially in requiring to be given by injection and in giving rise to unpleasant subjective symptoms. It remains for future research to find a means of prolonging its action and minimizing its side-effects.

Summary

The chemistry and pharmacology of T.E.A.B. are described.

T.E.A.B. produced a slight fall in gastric acidity in the secretory response to an alcohol test meal.

It negatived the secretory response to hypoglycaemia.

It reduced the response to histamine.

It reduced the volume and acidity of the 12-hour spontaneous night secretion.

It produced a vagotomy-like effect on gastric motility.

Its effect on the cephalic and humoral phases of secretion is discussed after its use in 10 patients submitted to insulin and histamine stimulations respectively. The changes in the concentration of the night secretion in 10 ulcer patients and the effects on motility in five ulcer patients are discussed; a comparison is drawn with that following vagotomy. Its disadvantages are enumerated. Experimental use in peptic ulceration in animals is mentioned and suggestions are made for further use.

We are indebted to Professor C. F. W. Illingworth (under whose guidance this work was done) for help in the preparation of this paper. We wish to thank Mr. A. W. Kay for facilities in recording gastric motility.

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NITROGEN MUSTARD THERAPY

WITH SPECIAL REFERENCE TO HODGKIN'S DISEASE

BY

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Therapeutic trials with the nitrogen mustards in cases of neoplastic disease were started in the United States in 1942. Rhoads (1946) published the first analysis of results obtained, and many further reports have appeared since. Experiences in this country have been given by ApThomas and Cullumbine (1947), Wilkinson and Fletcher (1947), ApThomas (1948), Boyland *et al.* (1948), and Watson and Pemberton (1948). These reports make no claim that the treatment is any more than palliative. The best results have been obtained in cases of Hodgkin's disease, and moderate but variable remissions in other lymphomata and lymphosarcoma, chronic leukaemia, polycythaemia vera, and mycosis fungoides. In carcinomatous conditions the results have been disappointing except in bronchial growths, where in some cases transient benefit has followed treatment. In April, 1946, a trial supply of the "bis" compound was received. As it is now generally available, this interim report summarizing the benefits and dangers attending its use is being published.

Dosage and Method of Administration

The amount of the drug that can be given is limited by the action on the bone marrow, and the American workers recommended that in a standard course the total dose of the "bis" derivative hydrochloride should be 0.4 mg. per kg. of body weight. This was divided into four doses of 0.1 mg. per kg. given intravenously on consecutive days. The vein used for the injection often becomes thrombosed, and to reduce the demand for veins trials were made with fewer but larger injections. This also

had the advantage that the vomiting which followed most injections was repeated on fewer occasions and the course was completed more quickly. When a patient is being treated for the first time it is advisable to start with a small dose—0.1 mg. per kg. or even less in debilitated subjects—and if the response is satisfactory the course may be completed by two further injections of 0.15 mg. per kg. In subsequent courses two injections of 0.2 mg. per kg. are given, or, if it is decided to give maintenance injections at regular intervals, 0.2 mg. per kg. once only, every four to eight weeks. The maximum single dose given to any patient was 12.5 mg. It was found that the best time to give the injections was in the morning after a light breakfast. The question of the time interval that must be allowed before a course is repeated will be discussed later in relation to toxic effects on the bone marrow.

The white crystalline salt is dissolved in about 10 ml. of sterile saline immediately before injection. It must not be allowed to stand after being dissolved, as it undergoes hydrolysis and becomes inactive. All-glass eccentric-nozzle syringes have been used with a size 17 needle ; the injection may be given as quickly as the size of the needle permits. It was found that when the injection was made direct into the vein thrombosis occurred in about half the cases. This may lead to considerable difficulty if repeated courses are needed, and it is also advisable to retain one large vein in case blood transfusion is required later. An alternative technique of administration is to inject the drug into the tubing of a running saline drip, by which the incidence of thrombosis is much reduced. When a patient receives the drug for the first time, direct injection may be used, but if widespread thrombosis follows and further courses are likely to be indicated it is wiser to change to the drip-tube method. Veins partly occluded by tumour masses should be avoided. If any of the solution escapes into the subcutaneous tissue, oedema, redness, and discomfort appear in about 24 hours and may last several weeks.

Results

In many of the published reports success has been claimed if any regression of the tumour masses occurred after treatment. The regression may, however, be so slight or so transient as to be of no practical value, and may be unaccompanied by any improvement in the general condition. Stricter criteria have therefore been adopted in assessing this series. The results have been described as conspicuous benefit, moderate benefit, or failure. Conspicuous benefit is considered to have been obtained if a previously incapacitated patient is able to leave hospital and return to and continue in his normal occupation for at least three months ; moderate benefit—a remission of similar duration in which the patient is able to leave hospital and be about his home ; and anything less than this —a failure. Thirty-eight patients have been treated and a total of 61 courses and a number of maintenance injections have been given. The cases treated and the results obtained are shown in Tables I and II.

TABLE I.—*Summary of Cases Treated and Results*

Nature of Case	Number of Cases	Result		
		Conspicuous Benefit	Moderate Benefit	Failure
Hodgkin's disease:				
Previously untreated	6	2	1	3
Previously treated by surgery	1	1	0	0
Previously treated by *x* rays	14	2	0	12
Malignant lymphoma	3	0	1	2
Acute lymphatic leukaemia	1	0	0	1
Chronic lymphatic leukaemia	1	0	0	1
Lymphatic leukaemia with lymphoblastic lymphoma	1	0	0	1
Multiple myeloma	1	0	0	1
Carcinoma of bronchus	5	0	0	5
Carcinoma of rectum	1	0	0	1
Mycosis fungoides	3	0	1	2
Lipomelanic reticulosis	1	0	0	1

TABLE II.—*Duration of Remission in Cases showing Benefit*

Case No.	Nature of Case	Course No.	Duration of Remission	Classification	Remarks
3	Hodgkin's disease	N.M.1	5 months	Conspicuous benefit	
		N.M.2	3 ,,		
5	Hodgkin's disease	N.M.1-2	12 ,,		On maintenance therapy for six months subsequently
		N.M.3	4 ,,	,, ,,	
		N.M.4	1+ ,,		
6	Hodgkin's disease. Surgical excision	N.M.1	21 ,,	,, ,,	
9	Hodgkin's disease. Previous *x* rays	N.M.1	6 ,,		
		N.M.2	3 ,,	,, ,,	
		N.M.3	3 ,,		
		N.M.4	Nil		
19	Hodgkin's disease	N.M.1	4 months	Moderate benefit	
		N.M.2	1 month		
24	Hodgkin's disease. Previous *x* rays	N.M.1	3 months	Conspicuous benefit	Three subsequent maintenance injections. Total remission 7 months
25	Malignant lymphoma	N.M.1	5 ,,	Moderate benefit	
		N.M.2	1 month		
10	Mycosis fungoides	N.M.1	8 months	,, ,,	
		N.M.2–3	3 ,,		

N.M. = Nitrogen mustard—the " bis " compound

Cases of Hodgkin's Disease that had not received Previous X-Ray Therapy.—In a group of six cases there were two in which conspicuous benefit was obtained. Both had visceral deposits, and one of them (Case 3) had fever and anaemia and the other (Case 5) amyloidosis and hypoproteinaemia. Case 19, with lymphadenopathy, fever, and anaemia, had a remission after the first course of four months during which she was able to leave hospital and do some of her housework ; a second course, however, produced less improvement and deep *x*-ray therapy was given. The three failures included one with anaemia, fever, and hepatosplenomegaly, which showed no response at all ; one with axillary lymphadenopathy, which rapidly recurred ; and one in which enlarged mediastinal glands showed slight regression only. The last two cases were examples of the commonest type of Hodgkin's disease, which presents with localized glandular masses, and on account of the poor results obtained here, and reported by others, no further cases of this type were given nitrogen mustard as the initial treatment. A further case (No. 6) had a large mass of glands excised from the side of the neck. Microscopical examination showed Hodgkin's disease, and a course of nitrogen mustard was given. The patient has remained well and been gaining weight since (21 months).

Cases of Hodgkin's Disease Treated Initially with X Rays.—The 14 patients who were treated initially with deep *x* rays and subsequently given nitrogen mustard fall broadly into two groups. The first (four cases, one conspicuous benefit (No. 24), three failures) had had repeated recurrences in one group of glands and the condition of the skin precluded further irradiation. The disease in patients of the second group had, after a slow or rapid evolution, apparently reached the terminal stage. In some, numerous deposits of Hodgkin's tissue were rapidly appearing in different sites ; in others, despite such evidence of activity as fever or anaemia, there were no deposits suitable for local *x*-ray treatment. (Ten cases, one conspicuous benefit (No. 9), nine failures.) In two cases of the more acute type in which the remissions produced by irradiation were of brief duration, those following nitrogen mustard were equally disappointing.

Results in Other Conditions.—There were three cases of malignant lymphomata of other types: a reticulosarcoma which showed no response, a very primitive lymphoma in which dramatic but incomplete and transient regression occurred, and a slow-growing lymphoblastic lymphoma in which there was moderate benefit (Case 25). In the cases of carcinoma of the bronchus treatment failed to relieve either chest or nerve-root pains. The three cases of mycosis fungoides were all of long standing, and although an incomplete remission of reasonable duration was obtained in one the results were disappointing.

Complications and Side-effects of Nitrogen Mustard Therapy

The three most important of these are: changes in the blood, vomiting, and venous thrombosis at the site of injection. The last-named has already been discussed.

The white cell levels changed in nearly all cases. In the first few days a transient increase of neutrophils and reduction of lymphocytes was usually found; much more important, however, was the granulopenia which followed —maximal at the beginning of the second week and returning to normal levels about the fourth. Complete absence of polymorphs from the peripheral blood occurred in two patients. The first had an acute malignant lymphoma, which showed partial regression after a course of treatment. As a desperate remedy this was repeated after two weeks, but the patient died one week later and the agranulocytosis which had developed was probably a contributory factor. The second patient had Hodgkin's disease, and derived some benefit from a course of nitrogen mustard, which was repeated after two months. Typical agranulocytic angina followed, but intensive penicillin therapy controlled the infection and white cells reappeared in the peripheral blood. He was later given a blood transfusion and was able to leave hospital, but he died at home shortly afterwards. In neither of these patients was the haematological response to the first course suggestive of unusual sensitivity, and the pre-treatment levels of polymorphs and lymphocytes were within normal limits in the first case and in the second were 3,900 and 260 per c.mm. respectively.

The depression of the white cell count is the limiting factor when the repetition of courses after a short interval is being considered. In the case mentioned above a second course was given as a desperate remedy after two weeks; on five other occasions a second course was given after four weeks without untoward result. With further experience this procedure was rarely adopted. If the clinical response to the first course is transient or incomplete little benefit may be expected from re-treatment at so short an interval; and if the patient is still in remission it is better to await evidence of renewed activity before undertaking a further course or starting maintenance therapy.

The use of nitrogen mustard therapy in cases of Hodgkin's disease with severe leucopenia has been discussed by Rosenthal (1948), who recommended splenectomy prior to treatment. The following case is of interest in this respect.

Case 5.—Man aged 26. Onset in June, 1944, with fever and enlarged axillary glands. Biopsy in January, 1947, showed Hodgkin's disease with amyloidosis; there were hepatomegaly, ascites, and oedema of the legs; Congo-red test gave 100% absorption, and serum albumin was 2.1 g. %. Two courses of nitrogen mustard at a four-weeks interval (26 mg. and 32 mg.) gave a good remission of twelve months' duration. In March, 1948, a relapse was treated with a further course of 25 mg., again with good response. In July a further relapse occurred and the absolute polymorph count was 128 per c.mm. Sternal puncture showed that 73% of cells were of the granulocyte series, and therefore a further course of 25 mg. was given, which led to a steady rise in polymorph counts. He received four maintenance injections of 12.5 mg. each and remained at work until December, 1948. He died in January, 1949.

The red cells were not usually affected when early cases of Hodgkin's disease were treated, unless the patient was anaemic, in which case a spontaneous rise to normal levels accompanied a good clinical response (Case 3). In terminal cases this treatment may produce extreme depression of the haemoglobin level, although it is difficult to decide to what extent this is due to the treatment rather than to the evolution of the disease. In the following case treatment was followed by an immediate improvement, but in the second week the patient became very anaemic, presumably as a result of the action of the drug on the bone marrow. The patient was, however, kept alive by blood transfusion and subsequently had a satisfactory remission.

Case 9.—Man aged 42. Onset August, 1944, with cervical lymphadenopathy; biopsy showed Hodgkin's disease, and a course of deep *x*-ray therapy was given. From April, 1946, to April, 1947, he had recurrent bouts of fever, for which he received further *x*-ray treatments and blood transfusions. He was then admitted to hospital, when examination showed him to be emaciated, febrile, and anaemic (Hb 60%), although there were no localized deposits of disease tissue. He was thought to be in the terminal stage of the disease. A course of nitrogen mustard (28 mg.) produced a dramatic fall of temperature and a great improvement in his condition and appetite. He left hospital a week later, but a fortnight after treatment he became very ill and had petechiae, and his haemoglobin was found to be 32%. A transfusion of 1 pint (570 ml.) of packed red cells was given and the level rose over a period of four months to 100%, and by then his general health was excellent. A further course of 25 mg. was given in November because his haemoglobin level had dropped to 86%; after the injections it fell to 60% but recovered spontaneously. Before this course his platelets were 300,000 per c.mm., but by the 15th day they had completely disappeared from the peripheral blood, and he had a few petechiae on his legs, although a capillary fragility test was negative. The pre-treatment level was not regained until eight weeks later. The remission after this course lasted until February, 1948, when a further 25 mg. was given. The haematological changes on this occasion were much less marked. He started getting severe pain in the neck in May, and local deep *x*-ray therapy brought considerable benefit. A further course was given in July; but this had no effect on the fever, which had recurred, and he died in September, 1948.

Platelet counts were not done in all cases, but in a few there was a pronounced fall during the third week after treatment, although purpura was seen in only one case (No. 9).

Nausea occurred in 80% of courses and vomiting in 70%. The latter started, often very suddenly, about three hours after the injection and lasted from two to six hours. It varied greatly in severity, and in three cases was so bad that the last injection of the course was omitted. It was worse after larger doses, but the increase was not marked. Pyridoxin and phenobarbitone were tried but had no significant influence. One patient in the terminal stages of Hodgkin's disease died 48 hours after an injection of 5 mg. She had rather severe vomiting, which probably hastened her death.

Discussion

There can be no doubt that malignant lymphomata, particularly the Hodgkin type, respond to nitrogen mustard therapy. This is shown clinically by regression of lymph nodes, spleen, and other deposits, remission of fever, and

improvement in strength, weight, and blood picture. It is nevertheless evident that this remedy is not curative, and to assess its value the length and completeness of the remissions which follow its use must be compared with those obtained by deep *x*-ray therapy—hitherto the only comparable form of treatment available. It is also necessary to take into account the particular difficulties of the therapy itself. In the case of the nitrogen mustards there are the dangers of the actions on the haematopoietic tissues and the discomforts of those on the gastro-intestinal tract. With deep *x*-ray therapy the duration of treatment is longer, the necessary apparatus must be available, and irradiation sickness and bone-marrow depression may occur.

The course of Hodgkin's disease is extremely variable. It may progress with all degrees of rapidity, and the prognosis cannot be correlated either with the histological appearances or with the clinical picture at any one time. Assessment of any therapy in this condition is therefore difficult, and can be attempted with confidence only on larger series of cases. It is possible to draw only the most tentative conclusions from a series as small as this.

In cases which present with localized glandular masses, nitrogen mustard therapy has not been found satisfactory, because the remissions are much shorter than those following irradiation.

In other cases, however, the disease is more generalized from the onset, with visceral involvement, fever, and anaemia. The *x*-ray bath technique is usually employed in these patients. The present series includes four cases of this type treated initially with nitrogen mustard; two responded well, one moderately, and in one the treatment failed completely. There were neither histological nor clinical features in the last case to explain the disappointing result. The first indication that the condition is responding is a dramatic fall of temperature after the first injection, and absence of such a fall is an ominous sign. The remissions obtained have been of reasonable duration and comparable to those following *x*-ray therapy. Visceral enlargement is a common feature of these cases, and irradiation is often followed by troublesome nausea and prolonged anorexia. With nitrogen mustard the treatment is completed in four days or less, and, although there is a temporary gastric upset, it soon passes and a good appetite develops if the condition is sensitive. It is in this type of case that further trials of nitrogen mustard therapy are particularly required before it can be decided which form of treatment is the more satisfactory.

In the late cases of Hodgkin's disease the problem is more difficult. In those in which there has been repeated recurrence of enlargement of the same group of glands the skin condition may prevent further irradiation and nitrogen mustard should be tried. In terminal cases a dramatic remission is occasionally obtained, and if the case is a chronic one it may be of reasonable duration. In the acute type, however, in which the condition has progressed rapidly, any remission is likely to be disappointingly short. The bone marrow is very susceptible in some of these cases and blood transfusion may be required. The decision to use nitrogen mustard in the terminal stage of the disease should be made only after careful consideration. The chance of an adequate remission is small, although an extra period of useful life may be gained in occasional cases. The patient is liable to have distressing vomiting, which may precipitate a fatal outcome, and severe leucopenia or anaemia is easily produced.

In the management of the typical case of Hodgkin's disease, presenting first with lymphadenopathy and after a slow evolution showing signs of generalization, both irradiation and nitrogen mustard may have their place. The glands should be treated initially with deep *x*-ray therapy, and after the first two or possibly three courses prolonged remissions may be expected. When the intervals get shorter or signs of generalization appear, the patient should be admitted to hospital and a full course of nitrogen mustard given. Complete blood and platelet counts are required at least once a week for four weeks to detect undue sensitivity of the bone marrow. If the response to this course is satisfactory, maintenance injections at four to eight weeks' interval may be used subsequently. These can be given to out-patients at the week-end without interfering with their work, but blood counts must be done before each one. If particularly troublesome local lesions appear at this stage, deep *x*-ray therapy should again be considered.

Summary

A preliminary report is made of the use of nitrogen mustard (the "bis" derivative) in a small series of cases over a period of three years. The dosage and administration of the drug are discussed. Serious haematological complications occurred in some cases, particularly those of advanced disease. Nausea and vomiting and venous thrombosis were troublesome side-effects.

Owing to the difficulty in assessing the degrees of response in such a variable condition as Hodgkin's disease the results have been classified as conspicuous benefit, moderate benefit, and failure. Benefit implies a three-months remission, with return to work in the first case and ability to return home and be about the house in the second.

Cases of Hodgkin's disease presenting with localized glandular masses respond better to radiotherapy than to nitrogen mustard.

Cases in which the disease from the beginning is widespread, involving the viscera, probably do better with nitrogen mustard than with irradiation.

Nitrogen mustard can be profitably used in some of the cases for which radiotherapy is no longer suitable. Surprisingly good results have been obtained at this stage in one or two patients whose disease had run a prolonged course.

I have to thank Professor H. P. Himsworth for guidance throughout this study, the staff of University College Hospital for allowing me to treat patients under their care, Dr. M. Maizels and his assistants for the extensive haematological investigations, and Mrs. E. L. G. Hilton, Director of the Radiotherapy Department at the hospital, who referred many of the patients for treatment and gave much useful advice. The original supply of nitrogen mustard was received through the Medical Research Council.

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As an introduction to the social welfare services in Britain the British Council arranged a two-weeks course in London during August for 17 holders of United Nations Social Affairs Fellowships from Argentine, Belgium, China, Egypt, India, and Sweden. The course included lectures by experts illustrated by visits in the London area. These enabled the students to see Queen Mary's Hospital, Roehampton, the Vauxhall Motor Works, Luton, and a housing estate at Bushey, Herts. At the end of the introductory course the fellowship holders followed individual programmes of study, planned by the British Council, on detailed aspects of social welfare such as the treatment and prevention of juvenile delinquency, the rehabilitation of the disabled, welfare among children and young people, and welfare in industry.

TREATMENT OF RINGWORM OF THE SCALP

BY

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The treatment of ringworm of the scalp by the application of preparations containing fungicides in various penetrating vehicles was the subject of an investigation by Brain *et al.* (1948). The best results were obtained with an ointment containing phenylmercuric nitrate 0.5% in a base consisting of "Crill No. 6," which is a non-ionizing surface-active compound, and "carbowax 1500" buffered to *p*H 4–5 by the addition of a solution of citric acid and sodium propionate. This investigation has now been extended to the use of salicylanilide in the same ointment base.

Salicylanilide is a white or pale-cream powder, very sparingly soluble in water, but soluble in alcohol and in the ointment base described above. Its use in the treatment of ringworm infections was first reported in America by Schwartz *et al.* (1946), who used an ointment containing salicylanilide 4.5%, hyamine 1%, and carbowax 1500 94.5%. Hyamine is a quaternary ammonium compound having surface-active properties, and was included to promote penetration of the fungicide into the hair follicle.

More recently the treatment of ringworm of the scalp with salicylanilide has been investigated in Scotland by Kinnear and Rogers (1948). These workers used an ointment containing salicylanilide 4.5%, cetrimide ("cetavlon") 1%, and carbowax 1500 94.5%. It is significant that they also used salicylanilide in a "eucerin" base, and found that it was no more effective than other ointments, whilst the conclusion was reached that salicylanilide in the carbowax base was the only preparation investigated which gave satisfactory results.

The following is the report on 27 cases of ringworm of the scalp treated with an ointment which has the following composition:

Salicylanilide	5 g.
Crill No. 6	10 ml.
Solution of citric acid 2% and sodium propionate 1%	2 ml.
Carbowax 1500	to 100 g.

Melt the carbowax 1500 over a water-bath, add the Crill No. 6, dissolve the salicylanilide in the mixture, add the solution of citric acid and sodium propionate, and allow to cool, stirring occasionally.

Instructions to Parents

The same technique of treatment was employed as in the previous cases. Parents were given written instructions and advised to follow them meticulously. The instructions were as follows:

1. Cut the hair of the entire scalp very short and keep it short throughout the treatment.
2. A linen cap should be worn day and night.
3. Wash the scalp every morning with soap and hot water and scrub the affected parts with a soft nailbrush.
4. Apply the ointment to the lesions with the help of a toothbrush and spread the rest of it into the entire scalp.
5. Report to the hospital should any undue irritation occur.

Remarks on Instructions.—(1) It has been found that whenever the mother failed to cut the hair of the entire scalp infected patches or individual hairs escaped the effect of the treatment. This made a prolongation of treatment necessary. (2) The linen cap prevented the spread of ringworm from infected pillows and hats, and protected the rest of the children in the family from contracting the disease. Several examinations of the inner side of headgears under Wood's light revealed the presence of fluorescing stumps. (3) We still think that mechanical friction is of considerable assistance in the elimination of infected hairs, the epilation being the preliminary step to any effective treatment of ringworm. Our further observations (see below) confirm that. (4) The toothbrush is an additional mechanical factor, and is also a good applicator. (5) Severe reactions such as kerion were not sought, and when these occurred parents were told to report as soon as possible in order to control the inflammation.

Parents were given enough ointment to last two to three weeks, and throughout the treatment the patients were seen only three or four times.

Clinical Picture

Every single case was diagnosed clinically, confirmed by Wood's light and microscopy, and the fungus in question identified by culturing. Both the course of the treatment and the follow-up were controlled with the help of a watchmaker's glass. In the experience of one of us (H. H.) it has proved indispensable in assessing the real progress of each case. It was interesting to watch the behaviour of the infected patches from the first day of the examination to the time of discharge of the case.

Under a watchmaker's glass by daylight an infected patch shows characteristic features which make a clinical diagnosis possible: the infected hair is broken, it has lost its elasticity, and it can be laid in different directions without returning to its previous position. It appears slightly darker, owing to the loss of the hair cuticle.

When looked at under Wood's light with the help of a watchmaker's glass the infected hairs appear brilliantly green, like the fluorescent dial of a wrist-watch, and the hair stumps lie loosely on the scalp but are still fixed in their follicles. When treatment has started, and the case is seen after a period of several weeks, a slightly different picture is presented. The hair stumps are polished off and the infected hairs appear now as brightly shining dots like stars on a dark background, and, when the case is responding, rarefaction of the patch is demonstrable. This rarefaction is due to the fact that a few hairs have already started to fall out, so that when the patch has become negative to Wood's light it does not mean that the affected hair has lost its fluorescence, but that epilation has occurred. As a matter of fact, a cured case shows the patch well polished and smooth, whereas a case which has not responded remains covered with hair stumps, and this fact can always be established by examining the patch with bare fingers. The lesions which have responded are smooth to the touch, whereas those that have not responded feel like a fine grater.

After a few weeks the empty follicles become filled with parakeratotic scales, and when such a patch is examined under Wood's light it seems as if the follicles contain white fluorescent hair stumps, indicating a relapse; but when removed with the help of forceps, placed on a slide with a drop of liquor potassae, and examined under the microscope it proves to consist of dried epidermis cells. Sometimes a few real white hair stumps were removed and proved to contain dry dead spores within them. They were of no significance.

Whenever pustulation or kerion formation occurred (which was accidental), both mechanical and ointment

treatments were stopped at once. A lotion containing acriflavine 1 in 1,000 with 10% tannic acid was applied until the lesions subsided. Crusting and scaling were treated with a sulphur-and-salicylic ointment. Individual infected hairs were dealt with by epilation with forceps.

The usual routine was to examine the patients every two, three, or four weeks. Once the case had become negative the mother was advised to continue with the treatment for another week, after which the treatment was stopped. A monthly follow-up for at least three months was necessary before the cases were discharged as cured, but we tried to extend surveillance as long as possible, and succeeded in a great number of cases in maintaining it up to five, six, or seven months.

Analysis of Cases

The accompanying Table gives a detailed account of the course of treatment of the 27 cases.

Cases of Microsporon felineum.—There were 20 cases in this group. Seven boys and 13 girls. The age ranged between 3 and 11 years. Fifteen cases were cured by salicylanilide alone. The time of treatment was between three and 14 weeks. Three cases, after having been treated with salicylanilide for ten weeks were given carbowax ointment containing phenylmercuric nitrate. They were cured in 7, 8, and 10 weeks. Two cases were epilated by *x* rays. Out of 20 cases, 15 responded and five failed.

Cases of M. audouini.—Six cases, all boys between 4 and 8 years; four were cured—two in six weeks, one in 12, and one in 16. Two cases failed, and were cured by *x*-ray epilation (75% cure, 25% failure).

Case of Trichophyton sulphureum.—A 6-year-old boy proved to be very resistant to local treatment, and after four months had to be referred to the radiotherapist for epilation.

Analysis of Cases

Case No.	Sex	Age	Mic.	W.L.	Cult.	Time Treated (Weeks)	Reaction	Cure	Follow-up (Weeks)	Cured by Other Methods
1	M	11	+	+	F	8	—	+	16	
2	M	10	+	+	F	5	—	+	20	
3	F	4	+	+	F	7	—	+	24	
4	M	10	+	+	F	3	Kerion	+	24	
5	F	3	+	+	F	6	—	+	24	
6	F	6	+	+	F	6	—	+	24	
7	F	7	+	+	F	4	—	+	16	
8	F	3	+	+	F	4	Slight folliculitis	+	16	
9	F	10	+	+	F	11	Pustulation	+	24	
10	F	3‡	+	+	F	5	Scurfy scalp; pustulation	+	24	
11	F	3	+	+	F	3	Small kerion	+	12	
12	F	5	+	+	F	14	Mild inflammation	+	28	
13	F	5	+	+	F	5	—		8	
14	M	7	+	+	F	5	Mild inflammation	+	16	
15	M	9	+	+	F	8	—	+	20	
16	F*	3‡	+	+	F	10	—	−		*X* rays
17	F*	5	+	+	F	10	—	−		,,
18	F†	5	+	+	F	10	—	−		Carbo 7 weeks
19	M†	7	+	+	F	10	—	−		,, 10 ,,
20	M	5	+	+	F	3	—	−		,, 8 ,,
21	M	7	+	+	A	6	—	+	20	
22	M	4	+	+	A	6	—	+	16	
23	M	7	+	+	A	16	—	+	5	
24	M	8	+	+	A	12	—	+	12	
25	M‡	6	+	+	A	10	—	−		*X* rays
26	M‡	4	+	+	A	10	—	−		,,
27	M	6	+	−	T.S.	16	—	−		,,

* Sisters. † Brother and sister. ‡ Brothers.
A = *M. audouini.* F = *M. felineum.* T.S. = *Tr. sulphureum.*
Carbo = Carbowax ointment containing 0·5% phenylmercuric nitrate.

Comment

There was local reaction in seven cases, ranging from mild folliculitis and pustulation to true kerion formation. All occurred in *M. felineum* cases, none in the *M. audouini* cases.

Comparison of the results achieved with phenylmercuric nitrate with those achieved with salicylanilide reveals very little difference. It is not the fungicide which effects the cure but the penetrating power of the bases employed. The latter bring about a softening of the hair and a loosening of the connexion between the hair and the hair papilla which effect epilation. Any fungicide will cure when the hair is removed. *X*-ray epilation has to be followed by the application of a fungicide.

We would like to point out that in no case have we seen healthy hairs fall out; the removable hairs were always proved to be infected.

In our previous paper we expressed the opinion that variance of response to treatment might be due to the individual resistance of the fungus to the fungicide. This may indeed be the case, but we would like to add another factor which may be important in influencing response to local treatment: that it is probably the hair itself which resists penetration of the base. From the table it will be seen that three pairs of brothers and sisters failed to respond to local treatment. In our opinion this may have been due to an intrinsic quality in the hair of the same family which was resistant to local forms of therapy.

Summary

A report is given on the treatment of ringworm of the scalp by the application of 5% salicylanilide in carbowax 1500.

Chemical properties of salicylanilide and the literature on its use in the treatment of ringworm are reviewed.

Twenty-seven cases—20 of *M. felineum* infection, six due to *M. audouini*, and one due to *Tr. sulphureum*—were treated.

Cure was effected in 75% of the cases.

No significant differences were observed between the responses to treatment of the human and of the animal type of ringworm.

The results obtained with salicylanilide in carbowax 1500 are practically identical with those achieved with carbowax ointment containing 0.5% phenylmercuric nitrate, as employed in our previous series.

We wish to express our thanks to Imperial Chemical (Pharmaceuticals) Ltd. for the supply of salicylanilide used in these investigations, and to Mr. R. C. Syms, chief technician at St. John's Hospital, for his valuable assistance.

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A proposal concerning the formation of a Department of Public Health in the Ministry of the Interior in Western Germany with, ancillary to it, an advisory council and a medical research council to deal with the standardization of drugs, vaccines, and sera is receiving favourable consideration by the German authorities, according to the July report of the Control Commission for Germany (British Element). As a result of a meeting in Geneva on June 1, 1949, at which a British and a German representative from Nordrhein-Westfalen were present, the World Health Organization has set up an International anti-Venereal-Disease Commission of the Rhine. This commission, consisting of experts on venereal disease from France, Holland, Belgium, Switzerland, and Germany—from the countries bordering the Rhine—with representatives of the Occupation Authorities of the Western Zones, made a technical study tour of the main venereal-disease treatment centres in the Rhine River area. This was the first step towards the co-ordination of the anti-venereal-disease services in the five countries concerned.

ASPIRIN POISONING

BY

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Reports of cases of aspirin poisoning, with the exception of those of Balázs (1930, 1931), have in the main been concerned with isolated instances and have discussed the clinical features, the difficulties of diagnosis, the post-mortem appearances, or therapeutic measures (Dyke, 1935; Wyllie, 1935; Neale, 1936; Charters, 1944). Hopkins (1945) was able to collect only 22 cases from the English literature during the years 1919–45, when he reported a case with recovery after the ingestion of 1,250 gr. (81 g.).

In the present paper the clinical features of aspirin poisoning are described from experience of 48 cases of attempted suicide with aspirin seen in the past two years. Two were fatal. These patients were all seen in the psychiatric wards of a general hospital serving, for purposes of Section 20 of the Lunacy Act, an urban population of about a million inhabitants. All cases of attempted suicide in the area notified to the police or to relieving officers before the National Health Act and to duly authorized officers since are brought to these wards, and therefore an unusual opportunity exists for observing a high percentage of the cases of attempted suicide in a large population.

From the figures presented in Tables I and II it is apparent that there has been a relative and an absolute increase in the number of cases of aspirin poisoning with suicidal intent in 1947 and 1948 in this area. During this period there were 48 cases of aspirin poisoning out of 284 cases of attempted suicide. The increase is mainly confined to females. Aspirin is the household remedy in most common use, and this ready availability is no doubt the most important factor in the increased incidence. Several other interesting points emerge from an examination of these tables. In males there was a higher attempted suicide rate over the period 1945 and onwards, whereas in females this increase did not occur until 1947. Before 1947 aspirin was used in about 10% of attempts at suicide in females, while over the past two years this figure has increased to between 20 and 25%. It has often been observed that attempts at suicide are relatively infrequent during the first quarter of the year. Table III illustrates not only this but also that, remarkably, no cases of aspirin poisoning occurred during this period of 1947 or 1948.

TABLE I.—*Incidence of Aspirin Poisoning: Males*

	1940	1941	1942	1943	1944	1945	1946	1947	1948
Aspirin poisoning ..	2	1	0	6	3	5	4	2	9
Total attempted suicide	47	37	27	39	37	61	81	57	65
Total admissions ..	447	337	343	363	366	348	350	320	315

TABLE II.—*Incidence of Aspirin Poisoning: Females*

	1940	1941	1942	1943	1944	1945	1946	1947	1948
Aspirin poisoning ..	0	2	7	4	7	3	4	16	21
Total attempted suicide	35	33	31	43	35	45	53	67	95
Total admissions ..	427	375	350	339	375	357	401	438	450

TABLE III.—*Quarterly Incidence of Attempted Suicide: Females*

	1947			1948		
	Total Patients	Attempted Suicide	Aspirin Suicides	Total Patients	Attempted Suicide	Aspirin Suicides
Jan.–March ..	110	9	0	104	17	0
April–June ..	112	18	6	130	40	12
July–Sept. ..	117	22	3	95	19	6
Oct.–Dec. ..	99	18	7	121	19	3
Totals ..	438	67	16	450	95	21

In the description that follows no special attempt is made to classify the cases according to the psychiatric manifestations. Hopkins (1937) described psychotic patients adopting self-mutilation, cut throat, hanging, immersion, and the caustic poisons for purposes of attempting suicide. The more bizarre the attempt the more questionable is the mental state. In my series of cases the psychic manifestations were in the main relatively mild.

No minimum fatal dose has been established, although most of the recorded deaths occurred within the range of 400–600 gr. (25.9–38.9 g.), but recovery has taken place after very much larger amounts. Hopkins (1945) reported 1,250 gr. (81 g.) (treated within three hours); Evans (1938) 1,500 gr. (97.2 g.) (treated within two hours); and in one of my cases 2,000 gr. (129.6 g.) (treated within five hours). In these three cases gastric lavage was performed early and powder was found in the stomach washings. In contrast to these cases, which recovered after early recognition and treatment, Biddle (1938) reported a fatal case with epileptic convulsions preceding death, which took place after 17 hours. The patient was a schizophrenic with delusions, and her story of having taken the aspirins was not believed.

Clinical Features

These are determined by two factors—excessive dosage and individual susceptibility. The earliest symptoms are mainly gastric and occur shortly after taking the drug. There is first a feeling of gastric discomfort, followed by pain in the epigastrium, nausea, and later vomiting. These symptoms are doubtless due to the direct irritant effect of the aspirin on the gastric mucosa (Douthwaite and Lintott, 1938). Aspirin is relatively insoluble, and large fragments will remain in contact with the gastric mucosa for a long time. The presence of an irritant in the stomach often leads to some degree of pylorospasm, which will delay the passage of the aspirin. This explains the finding of aspirin powder in the stomach after the normal emptying-time, and the value of gastric lavage up to many hours after the ingestion of the tablets.

Giddiness, tinnitus, and deafness occur later, and in the average case last for as long as 48–72 hours. The face often shows a blotchy erythema with some oedema, especially around the eyes. Profuse perspiration has been a constant finding. The patient is literally bathed in sweat until the toxaemia is overcome, and is very restless and resentful of interference. In Hopkins's (1945) case hallucinations occurred over a period of four days, but I have not met with this symptom. In more severe cases coma supervenes and the patient shows the features of shock, with subnormal temperature and low blood pressure. Renal symptoms have not played a prominent part in my cases, and I observed no abnormality apart from the presence of traces of albumin in the urine. Other authors have found greater evidence of renal damage. The speed with which treatment is usually possible may have some bearing on this finding. Haematemesis was not observed in my series. A pyrexia of up to 100 or 101° F. (37.8 or 38.3° C.) was often seen during the first 48 hours in severe cases.

Many of the clinical features are the result of acidosis with reduction of the alkali reserve. Respirations are deep

and rapid, but in spite of the apparent urgency of the respiratory embarrassment there seems to be little discomfort, and in no case has the patient complained of it. Severe or acute allergic reactions were not seen. The only findings suggestive of allergy were the slight oedema around the eyes and the blotchy erythema of the face. Dehydration, which develops if an adequate intake of fluids is not assured, is the result of the profuse perspiration and the rapid deep respirations.

Diagnosis and Prognosis

Diagnosis may be a difficult problem, especially where no history is available, and patients who have taken poison with suicidal intent may on occasion withhold this information even when conscious. One patient denied that she had taken any drug even after she had vomited material with the appearance of aspirin and giving the chemical reactions of acetylsalicylic acid. Aspirin poisoning should be considered when there is a blotchy erythema of the face with profuse perspiration and tachypnoea and tachycardia without distress, cyanosis of severe degree, and pathological signs in the heart or lungs.

Examination of the urine is a particularly valuable diagnostic measure. Aspirin is excreted in the urine as salicylic acid, which gives a purple colour with ferric chloride. To about 5 ml. of urine 10% ferric chloride is added drop by drop. A white precipitate of ferric phosphate is obtained and the urine then turns purple if salicylates are present. To distinguish this coloration from that produced by the presence of aceto-acetic acid, boil thoroughly 10 ml. of the urine, cool, and add ferric chloride. If the urine contains salicylates it will still give a purple colour; if it contains aceto-acetic acid there will be no colour change; and if it contains both substances the purple colour will be less intense than before (Harrison, 1947). Confirmatory tests are also described by that author.

In mild cases recovery is rapid, symptoms clearing in the first 48 hours. In the more severe cases coma may supervene and death may occur at any time during the first 72 hours. This is usually preceded by a rise in temperature; epileptic convulsions have been described, and stertorous or gasping respirations occur more regularly, with myoclonic twitching of the face and limbs. During 1947–8 there were two deaths out of the 48 patients seen. The first was the result of bronchopneumonia even though treatment was instituted early and the patient had been in good condition when first seen; in the second the patient was moribund on admission to hospital, having taken the aspirin almost three days previously.

During the period 1940–8 there were seven deaths associated with aspirin poisoning. Obvious pathological symptoms were present in two of these and the aspirin was only contributory. In the first there was a large cerebral haemorrhage, and in the second advanced generalized atherosclerosis with hypertrophy of the left ventricle and renal changes. Most of these seven patients had taken 500 gr. (32.4 g.) of aspirin, one dying after 400 gr. (25.9 g.) and another after 625 gr. (40.5 g.). In none of the seven cases had the patient been brought to hospital within the first twelve hours—i.e., during the period that gastric lavage would be of value. The majority were not seen until after the first 24 hours, and in two cases there was a lapse of at least 48 hours. The patients were either comatose on admission or rapidly became so after admission, and death occurred within five hours in three of the cases. The treatment in these cases included the use of stimulants (nikethamide, strychnine, etc.), drainage of C.S.F., intravenous fluids, and sodium bicarbonate. From the records available these measures do not seem to have greatly modified the clinical picture before death.

Briefly, the post-mortem findings have been those of an asphyxial death: cyanosis of the skin and viscera, petechial haemorrhages on serous surfaces, and congestion of the lungs. In one case bronchopneumonia developed on chronic bronchitis, and two others showed gross morbidity as indicated above.

Treatment

In general, early gastric lavage is the most important single therapeutic factor. All the measures advocated by Dyke (1935), Neale (1936), Oakley and Donnell (1942), and Charters (1944) have their place, depending on the clinical picture and the general condition of the patient. Although the degree of toxaemia inevitably depends on the amount of aspirin taken, subsequent clinical events bear a more direct relation to the speed with which treatment is instituted. If gastric lavage can be performed within the first few hours of taking the drug recovery can almost be assured. In the case described below 2,000 gr. of aspirin had been taken, yet the patient recovered, although she was dangerously ill for about 36 hours before improvement was apparent. In this connexion it is noted that all the deaths occurred in patients whose admission to hospital had been considerably delayed. Where this delay occurred treatment had no apparent effect on the patient's condition.

The bulk of the patients were brought to hospital within a few hours of taking the drug. Where the diagnosis was clear from the history—and a history was usually available—immediate gastric lavage was performed. A clinical impression is that washing the stomach with a weak solution of sodium bicarbonate is a better measure than using simple water. The stomach is washed until no trace of aspirin powder can be seen in the washings, and then, before the tube is withdrawn, one pint (570 ml.) of a solution containing 1% sodium bicarbonate is left in.

Later sodium bicarbonate is given in doses of 60 gr. (3.9 g.) at two-hourly intervals for a time and then four-hourly, depending on the clinical picture. If there is evidence of increasing acidosis two-hourly doses should be given, but as soon as acidosis is being overcome four-hourly doses are sufficient. In all but the deeply comatose—and this is a rare event if treatment is started early—the sodium bicarbonate can be given by mouth in water, soda-water, or milk. Fluids should be pushed to prevent dehydration. Shock is treated by the usual simple methods of warmth and intravenous fluids, the latter especially if there is any dehydration. Where there is evidence of vasomotor collapse with a pronounced fall in blood pressure "eucortone" or desoxycortone acetate is valuable.

The patient is made more comfortable with sponging, but care should be taken to prevent pulmonary infection, and penicillin should be given prophylactically until acidosis has been controlled. Where treatment as described above was adequately and speedily carried out, especially the gastric lavage, improvement was rapid, and within 48 hours the condition of the patient was good and such symptoms as tinnitus, deafness, tachypnoea, and excessive perspiration to all intents disappeared. It is doubtful whether intravenous sodium bicarbonate can influence severe and late cases. Lumbar puncture was used in such cases but only with other medication, and it is again doubtful whether the result was modified by this measure. A practical difficulty in carrying out lumbar puncture may be the

extreme restlessness and resistiveness of the patient, and an anaesthetic may have to be administered, which will increase the risk and is scarcely justified.

The following case report illustrates most of the features described above.

Case Report

A married woman aged 26 was brought to hospital at 3.30 p.m., having taken 400 tablets of aspirin about five hours previously. The dose of 400 5-gr. (0.32-g.) tablets was later confirmed by the patient on recovery and by police investigations. She had vomited once, and on arrival at hospital was very agitated and complained of severe ringing in the ears. Her general condition was good, but she was flushed and perspired freely. Her temperature was 98.4° F. (36.9° C.) and the pulse rate 100. The stomach was washed with a solution of sodium bicarbonate until the washings were clear, and 1 pint was left in the stomach. The early washings contained aspirin powder. Nikethamide, 4 ml. intramuscularly, was given. The heart, lungs, and C.N.S. were normal.

After this first-aid treatment she remained flushed, drowsy, and perspiring, and complained of tinnitus and deafness. The pulse rate increased to 120. Nikethamide and copious fluids containing 2% sodium bicarbonate were given throughout the night.

The following day her physical condition was not so satisfactory. There was much restlessness and profuse perspiration. Respirations were regular but forced at a rate of 28 per minute, the pulse thready and the rate rising to 130. Systolic blood pressure ranged from 80 to 90 mm. Hg. The diastolic pressure could not be recorded. Heart sounds were normal. Fine crepitations were heard over the anterior aspects of both lung fields. With the exception of absent knee reflexes the C.N.S. was normal. There was no abdominal tenderness and the liver was not palpable. The urine contained a trace of albumin, and tests for salicylates were positive. Penicillin was given prophylactically in addition to sodium bicarbonate, nikethamide, and fluids. On account of the low blood pressure 10 mg. of desoxycortone acetate was given and later repeated.

The next day her general condition was much improved. Her blood pressure was 100/60 and her pulse rate 115. The deafness and tinnitus gradually declined in intensity, and she made an uninterrupted recovery. Salicylates were excreted in the urine until the fifth day.

At no time had there been more than mild confusion of thought. Her mental state was one of severe depression.

Summary

There was an increase in the use of aspirin as an agent for attempting suicide in 1947 and 1948.

The clinical features of aspirin poisoning are described.

Treatment, with special reference to the value of early gastric lavage, is discussed.

A case of aspirin poisoning in which 2,000 gr. were taken, with recovery, is reported.

It is with pleasure that I acknowledge my thanks to Dr. F. Hopkins, consulting psychiatrist, Smithdown Road Hospital, for his constant encouragement, advice, and stimulation; to the nursing staff for their help; and to Dr. J. P. Steel, medical superintendent, for permission to refer to hospital records and to publish this report.

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HAEMATEMESIS AS A SURGICAL PROBLEM

BY

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In the past three years 150 patients have been admitted to the Royal Berkshire Hospital with gastro-duodenal haemorrhage. After excluding 15 patients who were known to have bled from tumours, oesophageal varices, etc., there remain 135 cases in which the haemorrhage was believed to be from an acute or chronic peptic ulcer. Their treatment forms the subject-matter of this paper. There were 10 deaths in the series. The cases were all admitted to surgical wards and were therefore regarded as potential surgical problems. Thirty-three patients were selected for surgical treatment, with two deaths.

There is still considerable difference of opinion about the part to be played by surgery in the treatment of this condition. This is partly due to a widespread belief that under medical treatment the mortality is very low, and partly to a concept that these patients cannot be treated surgically without a very high death rate. Avery Jones (1947), reporting on the results of his large series of cases so carefully treated and so fully investigated, has given us much new information and a very clear picture of the dangers of the disease with which we are dealing. There were 615 cases of peptic ulceration in his series, and the mortality was 7.8%. This is undoubtedly much lower than for the country as a whole; thus Lewin and Truelove (1949) have recently reported a 19% death rate from Oxford.

Avery Jones emphasized that we are dealing with two distinct and almost unrelated diseases—the acute erosion and the chronic ulcer—the most striking difference between the two conditions being in their respective death rates. He gives us the following facts with regard to medical treatment. (1) The mortality following haemorrhage from a chronic gastric ulcer is 20%. If bleeding recurs the mortality rises to 48%. (2) The mortality following haemorrhage from a chronic duodenal ulcer is 9% for males and 6% for females. If bleeding recurs this rises to 35%. (3) The risk of death falls almost entirely on patients over 40 years of age. (4) The acute ulcer has a very low mortality, but this rises to 7% if bleeding is recurrent. (5) Very severe recurrent haemorrhage may be caused by an acute ulcer.

From his results Avery Jones logically concluded that surgery might be indicated in "those patients, particularly over 50, with good clinical evidence of a chronic ulcer . . . who had brisk recurrent haemorrhage after admission."

Gordon-Taylor (1946) has long taught that surgery could save many lives if employed with discretion and skill and if supported by adequate blood transfusion. He pleads for early consultation with the surgeon in all cases where surgery might be of value.

Unfortunately, the results of surgery have not in the past been encouraging, and although Finsterer obtained a mortality of less than 4% by operating on all cases within 48 hours he could have achieved this only by operating on many patients who would have recovered without surgery. It is not justifiable to subject large numbers of patients to an unnecessary operation in order to save the few who would die without it.

In order that surgery may be used with good results in the treatment of haematemesis our aims should be to recognize those patients who are likely to die without operation, to recognize them while they are still fit to undergo the operation, and to make the operation itself a safe procedure.

Selection of Patients for Surgery

In this series surgery was considered if the haemorrhage was unduly severe, if the patient was over 40, if there was good evidence of a chronic ulcer, or if bleeding recurred after admission. Of these indications the first was by far the most important: the more severe the bleeding the more essential was surgical treatment considered to be. Usually at least two of these conditions existed before surgery was decided upon.

So far as was possible a decision was made at once. Sixteen patients were therefore operated upon a few hours after admission. In many other cases it was decided that operation should be performed if the bleeding recurred. These were the patients who were over 40 but who gave a somewhat indefinite history of dyspepsia, or patients whose haemorrhage did not appear to be severe enough to cause anxiety. The decision in the remaining cases was that medical treatment should be continued even if bleeding recurred. Three patients, all over 40 and all with a typical ulcer history, had lost a large amount of blood, but had lost it slowly. Although the haemoglobin was less than 50% the blood loss had never been rapid enough to cause a fall in blood volume—i.e., there had been no history of collapse and the pulse rate was 80. These patients were transfused slowly and were operated upon several days after admission. They are included in the results as cases treated medically, as the operation was not performed primarily for haemorrhage.

Blood Transfusion

Our experience is that transfusion does not increase the incidence of recurrent haemorrhage. There was therefore no hesitation in giving blood if the patient needed it. If transfusion is adequate at every stage of treatment so that the patient is never allowed to suffer severe depletion of his blood volume, then he can be maintained in a condition good enough to undergo an operation even after several days of repeated haemorrhages.

Our indications for transfusion were: massive haemorrhage—in preparation for operation; a raised pulse rate persisting after the stage of initial collapse had passed; a persistently low blood pressure even if the pulse rate was normal; and a haemoglobin percentage of less than 50.

It was unusual to find a low haemoglobin after a single haemorrhage. If it was less than 60% it was probably due either to a previous anaemia or to a previous haemorrhage. In such a case it was our practice to do no more than restore the blood volume in the first instance, even if the patient was to be operated upon. The anaemia could be corrected later by a slow drip of packed cells. In an average case the patient would enter the theatre after receiving three bottles of blood, with a fourth bottle dripping in slowly and available for emergencies. A haemoglobin estimation next day would show whether further transfusion was then required.

The Operation: Technical Details

It is usual for haemorrhage from an ulcer to be curiously intermittent. In no case in this series was active bleeding found on exploration, although several times manipulation dislodged a clot and caused bleeding to start. Gentle handling is therefore advisable.

A chronic ulcer is usually easy to find, although if of short duration it may be flat and not easily palpable and may show little external evidence of its presence. The acute ulcer will usually be detected only after the stomach has been opened. A finger or part of the hand introduced into the stomach will often find the ulcer. It is not usually the ulcer itself that one feels but the stump of the artery with a clot in it. It feels like a mustard seed. Failing this, it may be found by inspection. It is important to remember how often the acute ulcer is multiple; if an ulcer has no obvious blood vessel in it then it is not likely to be the source of the haemorrhage.

When the source of the bleeding has been found a decision is made on the best procedure to adopt. The chronic ulcer should usually be treated by gastrectomy. I doubt if there is any increased risk as compared with local excision, and it is the only operation likely to ensure freedom from trouble in the future. Excision of the ulcer can be a more formidable procedure than gastrectomy, especially with the high gastric ulcer that has penetrated the pancreas. The chronic duodenal ulcer which bleeds briskly is usually on the medial wall of the duodenum and penetrates the pancreas. The bleeding vessel is then either the gastro-duodenal or the superior pancreatico-duodenal artery. Haemorrhage from it can be controlled by underrunning the vessel above and below the bleeding-point.

Closure of the duodenal stump can be extremely difficult. Owing to the activity of the ulcer the tissues are friable and oedematous and the duodenum may have been slit up in order to expose the ulcer. Closure by the method of Yudin as described by Gordon-Taylor is probably safer than any other, but even so there is great danger of leakage. Two of these patients developed a temporary fistula.

In the past it has always been taught that speed was vital in these cases. My own experience has not confirmed this. In my hands the operation usually takes at least as long as does the "cold" gastrectomy, and neither the anaesthetists nor I have ever found the length of time to have any adverse effect.

These patients come into the theatre in very good condition and it is unusual to observe any deterioration during the operation. If the surgeon is in a frantic hurry with the patient *in extremis* then either the operation has been delayed too long or the resuscitation has been inadequate. A low mortality cannot be achieved in such circumstances. The patient should be fit enough to allow the surgeon to perform carefully an operation which will not only cure the haemorrhage but will give the patient a reasonable chance of freedom from further trouble.

TABLE I.—*Peptic Ulcer Haemorrhage, All Cases*

Diagnosis	Total		Medical Treatment		Surgical Treatment		Age Distribution		
	No.	Deaths	No.	Deaths	No.	Deaths	Under 40	Between 40 and 60	Over 60
Chronic G.U.	39	9	23	7	16	2	5	20	14
Chronic D.U.	41	1	33	1	8	0	12	17	12
Acute ulcers	48	0	43	0	5	0	8	23	17
G.J. ulcers ..	7	0	3	0	4	0	0	3	4
Total ..	135	10	102	8	33	2	25	63	47

Results

There were 10 deaths among the 135 cases in the peptic ulcer group—a mortality of 7.4%. Of the eight non-surgical deaths five could not easily have been prevented.

The other three patients could have been saved only by earlier transfusion or by surgery.

The age distribution, given in Table I, confirms the increasing incidence of this disease among older patients already shown in other recent series. This has an important bearing on the death rate. One would expect better results in a series with an unduly high proportion of young patients in it.

Thirty-three ulcer cases were treated surgically: 16 as soon as they could be prepared by transfusion, 13 because they had a second brisk haemorrhage, and four because prolonged medical treatment failed to control their haemorrhage. The ages of these four were 23, 24, 31, and 36. They were operated on because it was considered that nothing else would save them. The case history below is given as an example of unduly severe haemorrhages in a young man.

Case 15. Chronic Duodenal Ulcer.—This patient was an extremely fat man of 24 who had had attacks of dyspepsia at six-monthly intervals for five years. Just before his admission he vomited "two pints (1 litre) of blood." He looked very fit and his Hb was 80, but his pulse was 116. At the end of a 2-litre drip transfusion his pulse was 130 and he had vomited a great deal of blood and had had several melaena stools. Forty-eight hours after admission he had received by drip 6 litres of blood. His pulse was now 140. It was quite obvious that a vessel was bleeding faster than he could be transfused, and must be stopped. At operation I accidentally knocked the clot off the gastro-duodenal artery and started a haemorrhage which reminded me of a slipped renal pedicle. The torrent was soon stopped with two stitches, and a high gastrectomy was completed at leisure without his condition deteriorating further. The 3 litres of blood used in the theatre and afterwards brought the total to 9 litres.

TABLE II.—*Chronic Gastric Ulcers Treated Surgically*

Case No.	Age and Sex	Prev. Hist. (Yrs.)	Prev. X-ray Films	Prev. Haem.	Blood (litres)	Operation	Ulcer	Result
17	54 M	Many	—	—	1½	Same day	Multiple small	R.
18	47 M	1½	G.U.	—	2	" "	Small	"
19	64 M	29	G.U.	—	2	" "	Large, into pancreas	"
20	60 F	5	—	5 yrs	2	" "	Large	"
21	46 M	3	G.U.	—	2	Next morning	Large, into pancreas	"
4	47 M	5+	—	4 yrs	3	Same day	Large	Died
22	53 F	20	—	1 yr	4	Next day	"	R.
1	23 M	5 wks	—	—	7	"	Small	"
23	38 M	3	Neg.	2 yrs	3	Two days later	Large	"
24	46 M	2	Neg.	—	8	" "	"	"
3	55 M	Many	G.U.	—	6	" "	Large, into pancreas	"
2	36 F	Very slight	—	—	2	Bled for 5 days	Small	"
5	45 M	14	—	—	7		Large, into pancreas	Died
25	56 M	1	G.U.	6 mths	3	Same day	"	R.
33	62 M	Many	—	—	4	Next morning	Large	"
34	57 F	Many	—	—	3	For 2nd haemorrhage	"	"

R. = Recovered.

The Chronic Gastric Ulcer Group

Of the 39 cases in this group 23 were treated medically either because they were not considered fit for surgery or because the haemorrhage was not dangerously severe. Of these medical cases eight subsequently required gastrectomy. The 16 surgical cases were all treated by gastrectomy, the operation being technically easy in most of them and the ulcer usually easy to find. The bleeding vessel in all cases but two was a branch of the left gastric artery eroded in the subserous fat on the lesser curvature. The surgical deaths both occurred in this group. In neither case was death attributable to the fact that the operation had been performed in the presence of haemorrhage.

TABLE III.—*Chronic Duodenal Ulcers Treated Surgically*

Case No.	Age and Sex	Prev. Hist. (Yrs)	Prev. X-ray	Prev. Haem.	Blood (litres)	Operation	Comment	Ulcer	Result
26	54 M	5	D.U.	—	2½	Same day	—	Into pancreas	R.
27	31 M	5	—	—	5	After 3 weeks	Continued to bleed	"	"
15	24 M	5	—	—	9	After 3 days	"	"(G.D.A.)	"
28	53 M	4½	Neg.	—	7½	After a week	"	"	"
29	47 M	15 (Perf.)	—	—	3	Same day	Massive haem.	"(G.D.A.)	"
30	67 M	5	D.U.	—	6	" "	"	"	"
31	42 M	1	—	—	3	After 3 days	Continued to bleed	Small "	"
32	62 F	4 (Perf.)	—	—	2	Same day		"	"

G.D.A. = Gastro-duodenal artery. R. = Recovered.

The Chronic Duodenal Ulcer Group

There were 41 patients in this group and eight were treated surgically. They all recovered after partial gastrectomy. Three of them were desperately severe cases whose recovery under medical treatment would have been very unlikely.

Case 30.—This patient, a man aged 67, did not start to bleed until the day of his admission, and when he arrived he was so collapsed that it was doubtful whether he would survive long enough to be transfused. No pulse was palpable and no blood pressure could be recorded. Four hours later he was fit enough for the theatre. Operation revealed the gastro-duodenal artery lying exposed in a duodenal ulcer crater in the pancreas. It was underrun and a gastrectomy was performed. He was very ill for some days owing to leakage from his stump, but soon made a rapid recovery. He received 6 litres of blood, most of which was required to replace what he had lost during the short time he was bleeding.

TABLE IV.—*Acute Gastric Ulcers Treated Surgically*

Case No.	Age and Sex	Dyspepsia	Prev. Haem.	Blood (litres)	Operation	Comment	Result
9	40 F	None	2	3	Next day	Had bled previously	R.
10	59 F	Slight	—	2	After 4 days	Continued to bleed	"
7	52 F	"	—	1½	After 2 days	Chronic ulcer suspected	"
6	43 M	4 years	—	2	Same day	" "	"
8	40 M	3 "	Many	1½	" "	Had bled previously	"

R. = Recovered.

The Acute Ulcer Group

This common lesion of the stomach or duodenum was the cause of approximately one-third of the haemorrhages admitted to hospital. The diagnosis is not always correct, being based largely on negative evidence and subsequently confirmed in most cases by a negative radiograph. It is a lesion probably rapid in its development and similarly rapid in its healing. The vessels by which it bleeds are the arteries of the submucosa. Most of these vessels are small, and the involvement of a large vessel is probably a chance affair determined by the accident of the site of the ulcer.

TABLE V.—*Operations for Haemorrhage Following Gastro-jejunostomy or Gastrectomy*

Case No.	Age and Sex	Date and Nature of Operation	Ulcer	Blood (litres)	Treatment (Same Day)	Result
13	49 M	1924, Gastro-jejunostomy	Small Chr. G.U.	1	Gastrectomy	R.
14	42 M	1946, Gastrectomy	Large Chr. G.J.U.	3	2nd Gastrectomy	"
12	66 M	1916, Gastro-jejunostomy	Large Chr. G.U.	½	Gastrectomy	"
11	63 M	1924, " "	Acute G.J. ulcers	2	G.J. undone	"

R. = Recovered.

As these ulcers respond so well to medical treatment, and as they would never require surgery if they did not bleed, operation should be undertaken only in order to save life or because a chronic ulcer is suspected. If they are operated upon, local excision would be the best procedure if one could be sure that there was only one ulcer and if it is likely to be technically easy. All the 48 patients in this group recovered. There were five surgical cases, four of them being treated by gastrectomy.

Gastro-jejunal Ulcers

The diagnosis of gastro-jejunal ulcer was made clinically in patients who had had a previous operation—either a short-circuit or a gastrectomy. This diagnosis was sometimes wrong, but it is used as a convenient one for this group, which presents a special problem for the surgeon, who has to weigh the fact that a chronic ulcer is almost certainly present and demanding surgery against the added difficulties and dangers of a complicated resection. Of the seven patients in this group three bled from the original gastric or duodenal ulcer for which the short-circuit had been performed and one from an acute jejunal ulcer. The recovery of the four surgical cases was largely due to early operation. They were all operated on very soon after admission.

Case 14.—This patient, a man aged 42, was known to have a large gastro-jejunal ulcer which had followed an inadequate gastrectomy for duodenal ulcer. He was extremely collapsed and actively bleeding when he was admitted. To make him fit for operation 2½ litres of blood were required. Exploration revealed an enormous gastro-jejunal ulcer which penetrated deeply into the pancreas. In the base of the ulcer was a large artery with a fresh thrombus in it. A further 2 in. (5 cm.) of stomach was resected, and a fresh anastomosis was formed. A year later he underwent his third gastrectomy (and vagotomy) for another ulcer, which this time eroded deeply into the liver.

Other Cases.—Two patients not included in the series were treated surgically. One had a large carcinoma and recovered well after a total gastrectomy. The other patient bled profusely a week after the suture of a perforated gastric ulcer. He died after a long, tedious resection.

Summary and Comment

For several years all patients suffering from haematemesis or melaena admitted to the Royal Berkshire Hospital have been treated in the surgical wards. In the last three years 135 patients with peptic ulcer haemorrhage have been so treated, with a mortality of 7.4%. Under the age of 40 there were no deaths, no women died, and no patient died from an acute ulcer. Thirty-three patients were treated by operation, with two deaths. Although some patients were treated medically and some by surgery the principle of treatment was the same in all cases, and no comparisons can or should be made between the medical and the surgical results. This principle was that each patient was considered as a potential surgical case and was operated upon as soon as his life appeared to be endangered by his complaint. If surgery is to be used in this way it is justifiable only if a low surgical mortality can be achieved. A low mortality is dependent on careful judgment in the selection of cases, adequate and efficient transfusion, and early operation.

It was in consultation with Dr. John Mills, director of the pathological department, that most of these patients were treated, and I would like to express my gratitude to him both for this help and for the efficient transfusion service that he maintains. I am also grateful to my colleagues, who allowed me to treat these patients in my wards.

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IONTOPHORESIS IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE

BY

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Among the methods of treatment designed to overcome vasospasm or to produce vasodilatation in peripheral vascular disease the use of choline derivatives is suggested by the work of Dale and Gaddum (1930) and Dale, Feldberg, and Vogt (1936). Acetylcholine is unstable and rapidly hydrolysed in the tissues (Renshaw *et al.*, 1938). Its action on the autonomic nervous system is a double one, producing both muscarine- and nicotine-like effects. Some of its esters do not share these defects, and in this study we have been able, using the method of ion transfer, to compare the actions of the anions of two substances: acetyl-β-methylcholine ("mecholyl" and "amechol") and carbaminoylcholine ("carbachol," "doryl," and "moryl").

Pharmacology

The action of carbaminoylcholine, the official name of which is carbachol, resembles that of acetylcholine, but is more prolonged. The Simonarts (1934) showed that its nicotine-like action was stronger than in the case of acetylcholine. Fraser (1938) pointed out that its action on the cardiovascular system passes off in 30–40 minutes, though its effect on the gastro-intestinal tract and urinary bladder may persist for several hours.

Acetyl-β-methylcholine also has a relatively prolonged action, and Simonart (1932) showed that the methyl-group substitution deprived acetylcholine of its nicotine-like action. Its effects, in contrast to those of carbachol, are most pronounced on the cardiovascular system.

The method of ion transfer has been shown by Kovacs (1934), Saylor, Kovacs, *et al.* (1936), and Kramer (1937) to be superior in peripheral vascular disease to oral, subcutaneous, and intramuscular administration of compounds of this type. Montgomery, Holling, and Friedland (1938) determined by direct (plethysmographic) measurement the increased blood flow produced in the limbs of normal subjects by mecholyl iontophoresis, and their results fully confirmed the belief that this treatment effected dilatation of blood vessels specifically in the treated part. It is a further advantage that such unwanted general effects as micturition, defaecation, salivation, and bronchial spasm are much diminished when parasympathetic stimulants are given iontophoretically.

Method

The technique of Kovacs, Saylor, and Wright (1936) has been employed throughout. Reinforced asbestos paper is saturated with a 0.5% solution of the substance to be used and wrapped round the leg or thigh. A malleable metal plate, connected to a positive galvanic pole, is placed over this and held in position with a rubber bandage. A large flat electrode moistened with normal saline is placed under the back and connected to the negative pole. The electrodes should not be applied over any raw or inflamed areas or over recent scar tissue. The skin should always be protected by the asbestos paper from direct contact with the metal electrodes, so that burns may be avoided.

The current is turned on gradually at the beginning of each treatment and reduced slowly to zero at the end. A current of 5 mA passing for five minutes is used at the first session, these figures being gradually increased on subsequent occasions, but 30 minutes' treatment at 30 mA is not usually exceeded at any one time. The most useful warning of overdosage is the patient's reaction. Any more than a slight redness or sweating of the part treated is an indication for stopping treatment.

No rigid rules can be made for frequency of treatments, though thrice weekly was most usual in our cases. Duration of therapy is determined by the patient's response; but where treatment has been given over a period of three to four weeks without benefit the method is unlikely to be of value.

Severe general parasympathetic effects may conveniently be dealt with by an injection of 1/100 gr. (0.65 mg.) of atropine sulphate. Bronchial asthma, hyperthyroidism, and recent cardiac infarction are all contraindications to iontophoresis with these substances.

intervention was necessary. Satisfactory or partial improvement was seen in 56 cases (67%). A general survey of the table shows clearly that better results were obtained by the use of acetyl-β-methylcholine (Groups I and III) than with carbachol (Group II). The eight cases of senile gangrene were relatively resistant to iontophoresis with either compound, and similarly disappointing results were found in Raynaud's and Buerger's diseases and in acrocyanosis, but the number of cases was too small to allow any conclusions to be drawn. It is likely that some of these cases were more suitable for sympathectomy. We were unable to confirm the good results of Murphy (1937) in the treatment of thrombophlebitis by this means, and have latterly abandoned it.

The most satisfactory results were seen in 24 cases of intermittent claudication and 21 cases of diabetic gangrene. Improvement was observed in 19 cases of the former (79%) and in 16 cases of the latter (76%).

From our results we cannot infer, as did Kramer (1937), that iontophoresis with parasympathetic stimulants produces its best results in vasospastic cases. The great majority of our cases of intermittent claudication and diabetic gangrene showed mural calcification of the vessels radiologically, and we feel that this finding should not be regarded, as it often is, as a contraindication to the iontophoretic use of such compounds. It is our firm belief that this method is applicable, in the first instance, to all cases of peripheral vascular disease. Our aim has been, by perseverance with the treatment, to avoid the need for surgery or to reduce to a minimum such operative measures as may eventually prove necessary.

Condition	Group I (1938–41)				Group II (1941–6)				Group III (1946–8)				Totals
	No. of Cases	Improvement			No. of Cases	Improvement			No. of Cases	Improvement			
		Satisfactory	Partial	Nil		Satisfactory	Partial	Nil		Satisfactory	Partial	Nil	
Arteriosclerosis:													
Intermittent claudication	5	3	1	1	8	2	4	2	11	5	4	2	24
Senile gangrene	4	0	2	2	3	0	1	2	1	0	0	1	8
Gangrene in diabetes mellitus	10	6	4	0	3	1	1	1	8	2	2	4	21
Painful vasospasm ..	0	—	—	—	3	0	3	0	5	3	2	0	8
Raynaud's disease	1	0	1	0	2	0	0	2	1	0	1	0	4
Buerger's disease	1	0	0	1	1	0	0	1	0	—	—	—	2
Thrombophlebitis	6	2	1	3	7	1	2	4	0	—	—	—	13
Acrocyanosis	3	0	2	1	0	—	—	—	0	—	—	—	3
Totals	30	11	11	8	27	4	11	12	26	10	9	7	83

Results

Numerous workers, particularly in America, have obtained good results in peripheral vascular lesions. Kramer (1937), using mecholyl iontophoresis in 30 cases of various types, observed beneficial results in 22. Murphy (1937) treated 33 cases of thrombophlebitis by the same means, and found substantial improvement in 31. Ready healing of associated varicose ulcers was seen. Saylor, Kovacs, *et al.* (1936) obtained satisfactory results in 23 out of 26 patients with varicose ulcers.

The present series, comprising 83 unselected cases, covers the period from 1938 to 1948. The cases are divided into three almost equal groups by the exigencies of the recent war. Having used mecholyl from 1938, we were deprived of it in 1941 and used doryl, moryl, and carbachol as substitutes. It was not until 1946 that acetyl-β-methylcholine again became available as amechol.

The standard adjuvant treatment given to these patients consisted of rest, warmth, and antiseptic measures where necessary; in cases of diabetes mellitus the blood-sugar level was kept within reasonable limits. The patients were usually in bed, though the majority of cases of intermittent claudication were treated as out-patients. The results obtained are detailed in the accompanying table.

Discussion

The method of treatment described cannot be regarded as an isolated piece of therapy, nor is a cure claimed in any case. The pathological basis of most of these conditions is patently irreversible.

Improvement was judged to be satisfactory when either all symptoms disappeared or only minimal local surgical

Summary

The treatment of 83 cases of peripheral vascular disease by iontophoresis is described. The greater value of acetyl-β-methylcholine for this purpose is shown.

This work could not have been undertaken without the unfailing help of Miss A. M. Clark and Miss A. Fazakerley, successively heads of the department of physiotherapy at the David Lewis Northern Hospital.

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Medical Memoranda

A Case of Cutaneous Horn of the Arm

Cutaneous horns of varying sizes are described in the literature. The largest that I have found recorded is the case of Dr. Herman Carache, mentioned in Sutton and Sutton's *Introduction to Dermatology*. This was a scalp horn 8 in. (20 cm.) long, complete, but with a small base. The interest of the following case lies in the large size of the horn, together with its history and the unusual site from which it grew.

CASE REPORT

The patient, a man aged 53, sustained burns of the whole extent of the dorsum of the left upper arm and parts of the leg and back by a German flame-thrower in the 1914–18 war. The greatest loss of tissue was from the arm area, which was skin-grafted (heterogeneous Thiersch) from a nursing sister's thigh. He was in hospital for 18 months.

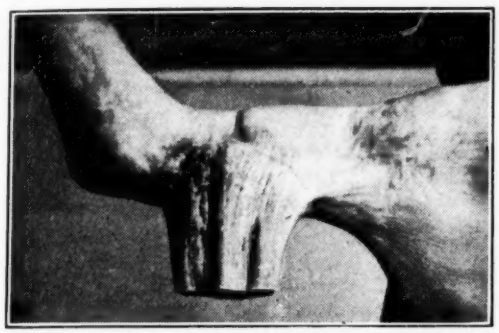

FIG. 1.—Showing extent and attachment of the horn.

The graft remained healed for twenty years, until 1938, when a minor injury to the arm broke the skin. This healed with simple treatment, but after a few months a tumour began to form at the site of this latter skin lesion. At first it was small—"the size of a hazel-nut"—but it steadily grew in base area and length. The direction of the growth was downwards in a curved manner. The tumour was painless, and when it became embarrassingly large the patient or his wife periodically cut off a piece with a hacksaw. Last year the medial side of the base became painful and forced the patient to seek medical advice.

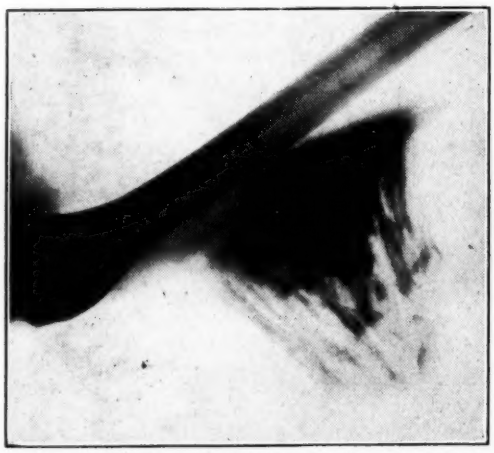

FIG. 2.—Radiograph faintly showing the horn.

On presenting himself at the out-patient department of this hospital the clinical findings were as follows: A large hard horny mass (Fig. 1) growing from a scarred area at the back of the left upper arm., tapering from an oval base; greasy surface longitudinally ridged; yellowish buff in colour; circumference of base 13 in. (32.5 cm.), length of horn 5½ in. (13.75 cm.), but it had been pared down. The cut surface had areas of dark discoloration and was similar in appearance to a sponge. The medial side of the junction of horn and skin was inflamed and tender and had signs of new extensions of the horn. The growth was movable over the deep structures of the arm. Skin-scarring extended in the posterior axillary fold and back of shoulder and elbow. Shoulder abduction was limited to 90 degrees; other movements were full. No axillary glands were felt. The patient brought with him a small bag containing the pieces he had sawn off. These numbered 17 and were of various sizes and similar in appearance and consistency to the main mass. A radiograph (Fig. 2) faintly showed the horn.

The growth was removed by Mr. N. Ross Smith and a skin flap was fashioned from the chest wall, which has healed well by first intention. At operation the base was found to be quite smooth and there was no infiltration.

The specimen has been accepted by the Museum of the Royal College of Surgeons, where the horn was patiently reconstructed from the main mass and the fragments (Fig. 3), showing what it might have looked like had it not been pared down by the patient.

FIG. 3.—The reconstructed horn.

I am greatly indebted to Mr. N. Ross Smith, under whose care the patient was admitted, for help and advice and permission to publish this case. My thanks are due to Mr. L. S. Allison for the first photograph, to the Curator of the Royal College of Surgeons Museum for the photograph of the reconstructed horn, to Miss M. Gall for the radiograph, and also to the patient for his helpful co-operation.

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Calcified Cyst of the Spleen

In the *British Medical Journal* of December 25, 1948 (p. 1106), Donovan described a case of calcified cyst of the spleen and stressed the rarity of the condition. It therefore seems worth while to record the following case.

CASE REPORT

The patient was a man aged 62 with no significant past history. He stated that for the last 12–15 months he had had a feeling of lassitude and gradually deepening depression. This was the feature of his illness which most affected him. His appetite was very poor and he thought he had lost several stones in weight in the past few months.

On examination he was seen to be grossly anaemic (haemoglobin 5.8 g. per 100 ml., red cells 4,100,000). In the right iliac fossa and hypogastrium a rather vaguely outlined fixed mass was palpable. No glandular enlargement could be made out. On deep inspiration the tip of his spleen could just be felt. It was firm in consistency. Radiologically the result of a barium enema was rather indefinite, but suggested a

neoplasm of the caecum. Owing to his general condition surgical intervention was considered to be inadvisable for the time being, but before there was sufficient improvement to warrant it he collapsed suddenly and died.

At necropsy, on opening the abdominal cavity a great quantity of serous fluid was found. A large solid tumour involving the caecum and invading the surrounding structures was also seen. There was a small recent perforation through the growth, shut off by adhesions from the rest of the peritoneal cavity. The tumour was immobile and quite inoperable. Histological sections proved it to be an adenocarcinoma.

The spleen contained, at its lower pole, a single cyst 4 cm. in diameter, with a calcified wall so hard that it necessitated bisection with a saw. It contained a few millilitres of rather iridescent yellowish fluid and many cholesterol crystals. The lower quarter of the cyst wall did not appear to be covered by the splenic capsule, nor was it adherent to adjoining structures. Histological section of the wall showed it to consist of hyaline and acellular fibrous tissue in an advanced state of calcification. There were no apparent changes in the spleen either adjacent to or remote from the cyst.

Other features noted at the necropsy were a moderate degree of atheroma of the aorta, arteriosclerotic kidneys, a cirrhotic liver, and bilateral bronchopneumonia. There was oedema of the meninges and subcutaneous tissue. Both pleural cavities and the pericardial sac contained serous fluid.

COMMENT

As in the case described by Donovan, no history of trauma was obtained. The splenic artery was not involved. The condition of the spleen, although it was just palpable, was discovered only at necropsy and seemed to have no bearing on the patient's illness.

No scolices or hooklets were found in the cyst fluid, nor was there an eosinophilia in the blood. Serological and sensitivity tests for hydatid disease were not carried out, as the condition was not suspected before death. The finding of cholesterol crystals suggests that the cyst was in fact an old haematoma, although no haematoidin crystals or other blood elements were seen.

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Volvulus of the Entire Small Intestine

Torsion of the mesentery of the whole small intestine is uncommon. I have been able to find accounts of only 61 cases in the literature.

CASE HISTORY

A male Bedouin Arab aged 35 complained that 14 hours previously he had suddenly been stricken with severe central abdominal colic which was followed by frequent vomiting at first of food and later of bile. The bowels had not been opened.

On examination he appeared dehydrated. Small quantities of bile-stained mucus were being vomited. The abdomen was distended and diffusely tender. Peristaltic sounds were absent. The hernial orifices were normal and rectal examination was negative.

I performed laparotomy at once (September 17, 1942) under open ether anaesthesia. Dark-red congested loops of small intestine appeared to fill the abdomen. The caecum was collapsed and much raised in position, but an empty loop of small intestine could not be found. The entire small intestine was therefore delivered without the incision. It could then be seen that there was a torsion of the whole mesentery, which arose from a deep trough of peritoneum, most striking in appearance. A deep vertical fold of peritoneum had been pulled up by the raised caecum from the right iliac vessels, while another deep ridge had been drawn down from the duodeno-jejunal flexure on the left side. The intestine was rotated counter-clockwise through three-quarters of a circle, thus restoring the normal axis of the mesentery, which was seen to be abnormally long. The gut was viable, so it was replaced and the abdomen was closed in layers. Saline was given subcutaneously and per rectum. Convalescence was uneventful.

DISCUSSION

The predisposing cause of volvulus is an abnormally long mesentery with a narrow base (Burgess, 1902 ; Dott, 1923). Volvulus is not rare in the newborn, especially in infants who already have a malrotation deformity of the intestine (Fletcher, 1922 ; Dott, 1927 ; Metzger, 1939 ; Voss, 1939 ; Thompson, 1940 ; Pouyanne, 1941). In adults, however, even if there is a congenitally long mesentery, some exceptional circumstance must initiate the twist. This is most often the ingestion of a large meal of coarse food on an empty stomach (Pupini, 1932 ; McKechnie and Priestley, 1936 ; Kerr and Kirkaldy-Willis, 1946). Shortly before the onset of symptoms my patient had consumed an enormous meal of mutton, rice, and unleavened bread after fasting from dawn till dusk, for he was a Moslem and the season was the feast of Ramadan. In Russia volvulus is commoner in times of famine (McClure, 1935). The activating mechanism may well be that a sudden body movement or strain causes a loaded loop of jejunum to descend by gravity, displacing lighter empty loops. This would accord with the fact that the direction of volvulus is clockwise in 75% of the recorded cases in which it is mentioned.

In diagnosis, repeated vomiting of small quantities of bile-stained material is stressed by Burgess (1902), Garrow (1917), Charsley and Richardson (1928), McClure (1935), Stalker (1939), Thompson (1940), and Barbosa (1944). Some of these authors state that faecal vomiting does not occur even late in this condition. In addition, the abdomen rapidly becomes silent to auscultation. The very quantity of distended congested small intestine is perplexing when the abdomen is opened at operation. Vaughan (1903) and Barbosa (1944) stress the difficulty of recognizing the condition at all, and point out that in at least four of the reported cases the surgeon was unable to discover the cause of the obstruction and closed the abdomen without remedying it. Diagnosis was made at necropsy.

Routier and Delbet (quoted by Vaughan, 1903) separately observed a peritoneal fold running upwards from the right iliac vessels similar to that which I have described. It therefore seems that without complete evisceration of the small bowel the diagnosis cannot be made or derotation be accomplished.

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Reviews

THE SURGICAL PATIENT

Care of the Surgical Patient. By Jacob Fine, M.D. (Pp. 544; illustrated. £2.) Philadelphia and London: W. B. Saunders Company. 1949.

This is not a textbook of surgery but a practical guide to the management of the surgical patient. It represents the practice of the Beth Israel Hospital in Boston. Associated with the editor are 22 of his colleagues, each of whom is responsible for a separate part.

The book is made up of six sections. Part 1, "General Considerations," includes such subjects as fluid balance, shock, and infections. Part 2, "Regional and Special Surgery," discusses abdominal, neurosurgical, orthopaedic, plastic, and dental surgery. Part 3 is on endocrine and hormone therapy, Part 4 on coincidental medical illnesses in surgical patients. Part 5 gives an account of clinical and laboratory methods, and Part 6 describes pre-operative and post-operative care. This last section contains articles on anaesthesia and the treatment of acute poisoning.

To the English reader certain terms require to be defined. What, for example, is a Zimmer collar (p. 79)? Or a Barton bandage (p. 106)? Or a Koenig-Rutzen bag (p. 155)? Illustrations would be helpful. Is it true to say that sooner or later the Brown-Séquard syndrome appears in cases of tumour of the spine or spinal cord? Except occasionally in the cervical region, this syndrome is rare in cases of cord tumour and is not often found on clinical examination. Frontal craniotomy is favoured for pituitary tumours; but the curious qualification is made that, "in case the field defect indicates congenitally short optic nerves, the transphenoidal approach is preferable" (p. 72). This requires explanation, as the transphenoidal approach has been so widely abandoned. Again, illustrations would be of value.

There are not many pictures in the text, and these have in many cases been borrowed from Hamilton Bailey, de Quervain, or others, and unfortunately lack text references. Objection is likely to be taken to the misleading association of Sir Gordon Gordon-Taylor's name with the statement (footnote, p. 116) that simple mastectomy combined with post-operative radiation gives the highest cure rate obtainable in cases of cancer of the breast. Most surgeons in this country still prefer to remove lymphatic nodes rather than irradiate them.

The field covered by this book is a large one; it is well ploughed in certain parts, but in others the surface is merely scratched. Its chief appeal will probably be to the students of the Beth Israel Hospital, whose teachers have provided them with a valuable guide-book and companion for their use in the surgical wards.

LAMBERT ROGERS.

NURSING IN NEUROSURGERY

Nursing Care of Neurosurgical Patients. By Roland M. Klemme, M.D., F.I.C.S., F.A.C.S. (Pp. 117; illustrated. 15s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1949.

The number of new specialties in surgery, with their increasing complications of technique, make it difficult to arrange adequate teaching of all branches within the limits of the medical student's curriculum. This is a serious problem with the student, but it is much worse with the trainee nurse. One solution is for her to acquire a good background of general principles and afterwards add the frills by a study of specialized monographs. For this purpose Dr. Klemme's small volume, based on his lecture notes, will be found very good indeed.

The book opens with a short but adequate account of the relevant anatomy, supplemented by diagrams from Gray and Kuntze. This is followed by a section on clinical signs and symptoms which is to be commended as simple, direct, and dogmatic. An article on the care of head cases is valuable for its excellent summaries of the nature and significance of various post-operative disturbances. The operations on the spinal cord and those performed for the neuralgias are well described in a similar manner.

Instruments and appliances are discussed at length in a separate chapter, with diagrams illustrating the best theatre layout. The details under this heading should be of great value to the nurse who is worried about preparation for a neurosurgical case.

Proof-reading has, as usual, failed to prevent an occasional misprint—there is a strange muscle, the "strapezius," on page 6—and here and there the book would gain by a translation from American into English. For instance, in a description of Parkinson's syndrome (p. 17) it is stated that "better than 85% are superimposed on encephalitis as a residual." After some cogitation the reader will no doubt decide that this means "more than 85% follow encephalitis."

While it is unlikely that other neurological surgeons will follow exactly all the technique described, the book is notable for its plain and explicit directions; the reader is never bemused by alternative methods or conflicting theories. This is a work which should be available for reference in any hospital which is out to do its best in the training of its nurses.

E. D. TELFORD.

AN AUSTRALIAN TEXTBOOK

Practical Obstetrics. By Bruce T. Mayes, M.V.O., F.R.C.S.Ed., F.R.A.C.S., F.R.C.O.G. (Pp. 306; illustrated. £2 5s.) Sydney: The Australian Publishing Co., Pty. London: George G. Harrap. 1949.

Professor Bruce T. Mayes's book is a series of clinical discussions on some of the important practical problems in obstetrics. The author had no intention of writing a complete textbook; his object was to explain and discuss the problems which are frequently encountered by Australian general practitioners. His topics have been wisely chosen, and he quite rightly emphasizes the striking work that was performed by N. M. Gregg in Australia on congenital cataract following German measles in the mother. Accounts of the diagnosis and management of pregnancy, toxaemia, eclampsia, and lower-segment caesarean section are well done, and the stress which has been placed upon the practical side is particularly praiseworthy. There is much evidence that Professor Mayes, as he acknowledges, has enjoyed writing the book, and it is certain that his work will be widely read and praised in Australia.

Great courage is required to write a book of this kind, for clinical opinions are open to criticism in detail, and this is particularly true of practical obstetrics. The Lövsett manœuvre is well described, though somewhat sketchily. Pudendal block should have been given greater prominence, particularly as the book is intended for general practitioners. Acute inversion of the uterus has been afforded a chapter, whereas more could have been written on the methods available for inducing premature labour. Drew Smythe's catheter—one of the most useful instruments in the practice of obstetrics—has not been mentioned.

Specialists should derive much pleasure from reading the book. The style is lively and many of the statements are provocative. There is much that can be criticized in detail, but the author holds one's attention from the first page to the last. The illustrations are of excellent quality, particularly the photographs of operations and demonstrations, and the line drawings merit special praise.

WILFRED SHAW.

PAEDIATRIC INVESTIGATIONS

Diagnostic Tests for Infants and Children. By H. Behrendt, M.D. (Pp. 529. £2 17s.) New York and London: Interscience Publishers Inc. 1949.

The procedures described in Dr. H. Behrendt's new volume are essentially tests for function. Convenient classification has been achieved according to the organ or system under investigation. Most sections begin with a brief description of the aim of the test succeeded by an account of the modifications caused by the age of the subject; then follow a note on procedure and an unusually large section on interpretation. Tests used at all ages are given little notice, and simple testing of the urine for

albumin is therefore omitted, except for a reference on page 159 which incorrectly refers to page 481. The space allotted to each subject is uneven, for much more attention is given to agglutination tests (which must be mostly the work of expert pathologists) than to those required in the control of dehydration in infancy. Apart from these criticisms the book will be warmly welcomed by clinicians concerned with the interpretation of tests. The index is adequate and the standard of production good.

ALAN MONCRIEFF.

ANAESTHETICS FOR CHILDREN

Pediatric Anesthesia. By M. Digby Leigh, M.D., and M. Kathleen Belton, M.D. (Pp. 240; illustrated. $5.50 or £1 7s. 6d.) New York and London: The Macmillan Company. 1948.

The budding anaesthetist has not long embarked upon his career before he finds that babies and young children do not behave like scaled-down adults but present many unexpected problems of their own. Babies develop obstructed airways at the slightest provocation, their tidal exchange is so small that the normal respiratory valves on gas–oxygen apparatus are unsatisfactory, and the absence of dead-space and avoidance of carbon dioxide build-up become of paramount importance. The smooth induction of anaesthesia is difficult, and the choice and introduction of tracheal tubes demand much consideration.

All these and many other matters are discussed admirably in this book, but the publisher's claim that it is the first on the subject is in error by over a quarter of a century. All forms of general, local, and spinal techniques are described in a lucid fashion, and ancillary subjects such as oxygen and fluid therapy are also discussed. The illustrations are good, but would be better if the features of the babies' faces had not been eliminated; as it is, an unnecessarily macabre effect is obtained.

C. LANGTON HEWER.

PLASTIC SURGERY

Surgery of the Hand. By Sterling Bunnell, M.D. 2nd edition (Pp. 930; illustrated. £5.) London: J. B. Lippincott. 1949.

Plastic Surgery of the Nose. By Albert P. Seltzer, M.D., F.A.C.S. (Pp. 305; illustrated. £3 12s.) London: J. B. Lippincott. 1949.

The early appearance of the second edition of Bunnell's work is a sufficient indication that surgeons as a whole share the opinion of the original reviewers and accept it as a standard textbook. The most obvious addition to the new volume is the inclusion of a chapter on tumours of the hand, but it is the rewriting of short sections in the main text that has added most to the value and completeness of the edition. Lesions of the hand likely to be met with by the average surgeon are all adequately described within its pages. It is no exaggeration to say that the increasing importance attached to the surgery of the hand derives largely from Bunnell's work, and it is to be hoped that this excellent volume will be available to all those who are called upon to treat the increasing number of hand injuries with which industry and the roads present us.

Approximately the first third of Dr. Seltzer's book is concerned with the anatomy of the nose and with the preparations which precede operation on it. The remaining two-thirds are occupied with descriptions and illustrations of operations for the correction of nasal deformities. More stress is laid on the correction of skeletal defects than upon reconstruction after losses of soft tissue, and for this reason the work is incomplete. Within its limited scope, however, it is a concise and accurate résumé of current practice.

RAINSFORD MOWLEM.

In *The Food of the People*, by Sir Noel Curtis-Bennett (pp. 320; illustrated; 16s.; London: Faber and Faber, 1949), the author traces the evolution of communal feeding in this country from the time of the mediaeval manorial manor to the modern industrial canteen. He is especially concerned with the variations in the attitude of employers towards their responsibility for seeing that their workpeople have the opportunities for obtaining a sufficiency of suitable food. The book is easy to read, well printed and well illustrated, and can be recommended as an introductory study for a young business executive eager to learn about his social responsibilities. Lord Woolton has added a preface.

BOOKS RECEIVED

[*Review is not precluded by notice here of books recently received*]

Psychosomatic Medicine. By E. Weiss, M.D., and O. S. English, M.D. 2nd ed. (Pp. 803. 47s. 6d.) Philadelphia and London: Saunders. 1949.

Oral and Dental Diagnosis. By K. H. Thoma, D.M.D., F.D.S. R.C.S.Eng. 3rd ed. (Pp. 563. 47s. 6d.) Philadelphia and London: Saunders. 1949.

Geriatric Medicine. Edited by E. J. Stieglitz, M.S., M.D., F.A.C.P. 2nd ed. (Pp. 775. 60s.) Philadelphia and London: Saunders. 1949.

Modern Discoveries in Medical Psychology. By C. Allen, M.D., M.R.C.P., D.P.M. 2nd ed. (Pp. 236. 12s. 6d.) London: Macmillan. 1949.

Careers in Local Government. By J. B. Swinden. (Pp. 180. 7s. 6d.) London: The National Association of Local Government Officers. 1949.

Science News 12. Edited by J. L. Crammer. (Pp. 160. 1s. 6d.) Harmondsworth, Middlesex: Penguin Books. 1949.

The Red Cross and the White. By H. St. George Saunders. (Pp. 195. 8s. 6d.) London: Hollis and Carter. 1949.

B.C.G. Vaccination in Theory and Practice. By K. Neville Irvine, D.M., M.A., B.Ch.Oxon., M.R.C.S.Eng., L.R.C.P.Lond. (Pp. 130. 9s. 6d.) Oxford: Blackwell Scientific Publications. 1949.

The Design and Equipment of Hospitals. By R. Ward, F.R.I.B.A., F.I.Arb., M.R.San.I. (Pp. 360. 42s.) London: Baillière, Tindall and Cox. 1949.

Clinical Auscultation of the Heart. By S. A. Levine, M.D., and W. Proctor Harvey, M.D. (Pp. 327. 32s. 6d.) Philadelphia and London: Saunders. 1949.

Nutrition and Diet in Health and Disease. By J. S. McLester, M.D. 5th ed. (Pp. 800. 45s.) Philadelphia and London: Saunders. 1949.

Confrontations Radio-Anatomo-Cliniques. By M. Chiray, R. A. Gutmann, and others. Vol. 3. (Pp. 78. 1,000 francs.) Paris: Doin and Masson. 1949.

Sémiologie Clinique. By P. Delafontaine and others. (Pp. 522. No price.) Paris: Flammarion. 1949.

Elements d'Anthropologie. By C. Chippaux. (Pp. 158. 600 francs.) Paris: Librairie Maloine. 1949.

Die Elektrokardiographie. By A. Weber. 4th ed. (Pp. 207. M. 18.) Berlin: Springer. 1948.

Nouveaux Procédés d'Exploration Fonctionneile du Rein. By J. Hamburger and A. Ryckewaert. (Pp. 155. No price.) Paris: Flammarion. 1949.

Les Métrites du Col. By P. Durel. 2nd ed. (Pp. 333. 650 francs.) Paris: Masson. 1948.

Untersuchungen über den Lumbalen und Cervikalen Wirbelbandscheibenvorfall. By F. Reischauer. (Pp. 87. M. 9.60.) Stuttgart: Georg Thieme. 1949.

Klinische Psychologie. By W. Hellpach. 2nd ed. (Pp. 234. M. 16.50.) Stuttgart: Georg Thieme. 1949.

Darmbrand. By K. Hansen, E. Jeckeln, J. Jochims, and others. (Pp. 212. M. 25.) Stuttgart: Georg Thieme. 1949.

Surveys of Anatomical Fields. By J. L. Shellshear, D.S.O., M.D., M.S., and N. W. G. Macintosh, M.B., B.S. (Pp. 172. No price.) Sydney: Grahame Book Company. 1949.

Die Schmerzverhütung bei Chirurgischen Eingriffen. By P. Moritsch. (Pp. 279. 48s.) Vienna: Wilhelm Maudrich. 1949.

La Fecondazione Artificiale nella Donna. By S. di Francesco. (Pp. 98. No price.) Milan: Istituto "La Casa." 1949.

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THYMECTOMY IN MYASTHENIA GRAVIS

To assess the results of a new method of treatment may require many years of painstaking observation, and when the disease is rare and with a course so unpredictable as that of myasthenia gravis the difficulties in assessment are great indeed. Myasthenia gravis was first described[1] by Willis in 1685. He attributed the disease to a "scarcity of the spirits," saying of these patients that "the stores of the spirits which influence the muscle being spent, they are scarce able to move hand or foot." To some it may seem that we can offer no more satisfactory explanation than Willis of the cause of this mysterious malady. While the disease is admittedly rare, recent advances in diagnosis and treatment have brought increasing numbers of cases of myasthenia gravis to light. The operation of thymectomy has undoubtedly provided the greatest stimulus of this kind. Sauerbruch performed the first thymectomy for myasthenia gravis in 1912, through a cervical incision; it was said to have improved but not cured the patient.[2] Sauerbruch undertook two further operations in patients with tumours of the thymus, but both died a few days later. Only one other thymectomy for myasthenia gravis was recorded up to 1937, when Blalock first published a series of six cases.[3] Subsequently he recorded his results in 20 cases,[4] but Mr. Geoffrey Keynes now has an experience of this operation which is unrivalled by any surgeon in the world. In the opening pages of this issue he reports the results of thymectomy in 155 patients, and his observations will be studied with profound interest. While admitting that the operation is in some ways empirical, he claims that the results obtained are better than those from any other form of treatment.

No clear-cut relationship between the thymus gland and the disease has been established. Though it has been suggested that the thymus forms a curare-like substance, Harvey[5] has stated that much of our present knowledge fails to support this suggestion. The tendency to remission in myasthenia gravis is well known; the remission may last as long as fifteen years, and the most satisfactory occur early in the course of the disease. This last point was mentioned by several speakers at a meeting in 1946, when a large number of cases operated on by Mr. Keynes were demonstrated, and it was suggested that it might explain the better results obtained in the cases of short duration. The assembly of so many cases of myasthenia gravis at the National Hospital, Queen Square, was an unusual spectacle, but it was a disappointment to some of those who examined them that so many of the cases were still taking neostigmine ("prostigmin"). Nevertheless, the remarkable improvement in some of the younger patients led several eminent neurologists to express the opinion that thymectomy represented a great advance in treatment. Early impressions of the results of operation emphasized the need for study of further series both of untreated cases and of cases treated only with neostigmine.

The clinical course of untreated myasthenia gravis was investigated by Kennedy and Moersch,[6] who reported 34 deaths in 87 untreated cases observed between 1915 and 1932. In the fatal cases the disease had been present for periods varying from six months to 22 years, with an average of 4½ years. The details of the remissions in the surviving cases of this series are referred to by Mr. Keynes, as also are those of a further series treated with neostigmine. The latter series, published by Harvey,[5] does not include comparable mortality figures, but no significant remissions were noted in patients who had been under treatment with moderate or large doses of neostigmine for more than six months. The fact that almost all of the present large series of patients had been treated with this drug makes the operative results all the more impressive. Many patients remain on neostigmine after operation; a few of them have required even larger doses than before, and this has sometimes been cited as an argument against thymectomy. Such criticism is not valid unless these cases are considered in relation to the partial and complete successes so that a comprehensive picture of the results of operation is obtained. The grading of cases adopted by Mr. Geoffrey Keynes has also been used by Blalock, and this ABCD classification is both reasonable and convenient. One of the most important criteria of successful treatment will be the maintenance of much the same relationship between these four grades, while a progressive promotion of cases from the lower to the higher grades, such as is suggested by this series, will be even more significant.

It is not easy to explain the failures in treatment. Operating too late in the disease is one possibility, and incomplete removal of the gland is another. It may be that some patients will never respond to thymectomy, but there is as yet no certain way of distinguishing them.

[1] Guthrie, L. G., *Lancet*, 1903, **1**, 330.
[2] Schumacher and Roth, *Mitt. Grenzgeb. Med. Chir.*, 1912, **25**, 746.
[3] Blalock, A., Harvey, A. M., Ford, F. R., and Lilienthal, J. C., *J. Amer. med. Ass.*, 1941, **117**, 1529.
[4] Blalock, A., *J. thorac. Surg.*, 1944, **13**, 316.
[5] Harvey, A. M., *Bull. N.Y. Acad. Med.*, 1948, **24**, 505.
[6] Kennedy, F. S., and Moersch, F. P., *Canad. med. Ass. J.*, 1937, **37**, 216.
[7] Bratton, A. B., *Proc. Ann. Meeting B.M.A.*, 1948, 159, London.
[8] Collins, D. H., *Proc. R. Soc. Med.*, 1946, **39**, 601.
[9] Sloan, H. E., jun., *Surgery*, 1943, **13**, 154.
[10] Trethewie, E. R., and Wright, R. D., *Aust. N.Z. J. Surg.*, 1944, **13**, 244.

Whatever may be the explanations for the failures, it must be admitted that treatment is beset with difficulties which are enhanced by our ignorance of the normal function of the thymus. On thymectomy for tumours it is interesting that Blalock, with his limited experience, felt that the indications were definite and the results satisfactory, whereas Keynes with his far greater experience is convinced of the very much worse prognosis in these cases. In the non-tumour cases the gland appears normal on inspection, but there are histological changes. Bratton[7] has stressed a qualitative difference in the islands of parenchyma and the formation of "germ centres" in the medulla. These appearances have been noted also by Collins[8] and by Sloan[9]; similar features were present in Blalock's cases, but it is impossible to say whether they are a cause or an effect of the disease, though they are seen only occasionally in the thymus in non-myasthenic cases. Several series published in the past and culled partly from necropsy records have contained an undue proportion of tumours of the thymus: the present series shows the true incidence of tumours to be in the region of 11.5%. Bratton has emphasized that the incidence of myasthenia gravis in cases of thymic tumour is about twice the incidence of thymic tumours in cases of myasthenia.

In the future fruitful investigations may be undertaken jointly by the biochemist and the experimental physiologist. It has been shown that the serum from a patient with myasthenia gravis will interfere with the transmission of an impulse in the ordinary muscle-nerve preparation,[10] but the real cause of this effect is unknown. Biological and chemical assay of the excised glands may yield further information on this and other points. While the results of fundamental investigations are awaited it is desirable that the treatment of these cases should largely be undertaken by a highly skilled few. The technique of thymectomy has been ably demonstrated by Mr. Keynes in a film, and he is to be congratulated on his low mortality rate. To suggest that only continued observation of this steadily growing series will provide further and much-needed evidence of the true value of operation is not to detract from the brilliance of the work already done.

AIR HYGIENE

The contrast has often been pointed out between the sanitary qualities of water and air in modern civilized conditions. That a water supply should be free from infection is now taken for granted, but the more difficult problem of ensuring that the air we breathe shall be equally innocuous is not only unsolved but until recent times was almost untouched. It began to be taken seriously during the middle 'thirties, and became a subject of intensive research in this country in the early part of the war, when conditions in air-raid shelters and elsewhere seemed to favour the spread of air-borne epidemics. A team of workers directed successfully by the late Sir Patrick Laidlaw, Dr. C. H. Andrewes, and Dr. R. B. Bourdillon carried out a comprehensive study of the whole subject of air disinfection, the results of which have now been published as a Medical Research Council report entitled *Studies in Air Hygiene*.[1] This is a lengthy monograph of 356 pages, containing a large amount of highly technical information as well as descriptions of experiments and assessments of their significance which will command wide general interest.

The first essential in any such work is an accurate quantitative method of determining the bacterial content of air, and for this purpose the slit sampler invented by Bourdillon and his colleagues is evidently superior to any other device, even among those used in very extensive studies of this subject which have been proceeding at the same time in the U.S.A. This ingenious machine has been perfected and modified for different purposes, and over 40 pages of the report are given to descriptions of the apparatus and its use. Its principle is that air is sucked at a known velocity through a narrow slit immediately above a slowly revolving plate of culture medium: particles containing bacteria impinge on the surface of the medium and adhere to it. The resulting colonies can be counted, and, since the volume of air sampled per minute and the speed of rotation of the plate are predetermined, the number of bacteria-carrying particles per cubic foot of air can be calculated. The great advantage of this method is that it immediately shows the effect of any change in atmospheric conditions: an "event" such as the shaking of a blanket is reflected in a high concentration of colonies in the sector of the plate exposed at that time.

The slit sampler has been used not only in many laboratory experiments and in studies of air contamination in hospitals, but in other field trials here reported for the first time. These include investigations made in private houses, factories, and in a cruiser and a submarine at sea in time of war. The liability of naval crews to air-borne infection is notorious, and this last study shows exactly where and in what conditions the overcrowding in the crew's quarters leads to excessive air contamination, despite vigorous ventilation. Curiously enough, the bacterial content of air in the submarine was consistently fairly low; possibly this is due to adhesion of bacteria-carrying particles to oily surfaces as the air circulates through the engine-room. On the basis of such studies it is suggested that 50 colonies per cubic foot of air on blood agar at 37° C. should be regarded as a limit not to be exceeded, and that such

[1] *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 262. London: H.M.S.O.

counts offer a better method than any other available of deciding whether the air of an occupied space conforms to a satisfactory hygienic standard.

The main object of most of the work described was to define efficient and practicable methods of disinfecting air which is inevitably contaminated. Tests of various methods are described in detail, followed by reasoned statements of their possible applicability in different conditions. Ultra-violet radiation has distinct spheres of usefulness, though owing to its incapacity to destroy bacteria in dust particles it may need to be combined with measures for dust suppression. Useful chemical reagents fall into four classes. Hypochlorous acid, liberated by spraying a sodium hypochlorite solution, is effective and can be disseminated by a hand-spray: its use in offices and other such buildings is considered worth while during an air-borne epidemic. Resorcinol and other related compounds are also effective and harmless, but act for only short periods. Triethylene glycol has been extensively studied in the U.S.A. and was not included in this investigation. The main contribution of the M.R.C. workers in this field has been to demonstrate the activity as air disinfectants of lactic acid and related compounds. Lactic acid itself, though harmless, is somewhat irritating, but α-hydroxy-α-methylbutyric acid is less so and has the advantage that it volatilizes adequately from an unheated surface of sufficient extent. If this substance becomes available in sufficient quantity practical trials of its use would seem to be well worth undertaking.

The keynote to the general conclusions of this report is that air disinfection is practicable only in special circumstances. There is no prospect whatever of the widespread adoption of any of these methods in public buildings and conveyances: such problems are almost insuperable, owing either to the great size of the task or to the variable conditions for which provision would have to be made. It is also emphasized that appliances used for this purpose are apt to be neglected: "people lose interest" in them, as is perhaps natural when the result of their use is at best only the negative condition of absence of infection. The nearest approach to large-scale air disinfection advocated here is the spraying of sodium hypochlorite in offices and workrooms during an epidemic, as already mentioned. It is, of course, recognized that much can be done in such places by good ventilation and lighting and by measures to suppress dust. Otherwise the indications for chemical or other special treatment of air are more or less restricted to the hospital and the laboratory, where known dangers have to be countered in a space of manageable size and in circumstances permitting full control. There is a great deal to be gained by applying these principles and methods to the control of hospital cross-infection alone, and the medical historian of the future is likely to rank the British contribution to progress in this subject as one of our main medical achievements during the war period.

NITROGEN MUSTARDS

Although the pharmacology, biochemistry, and chemistry of the nitrogen mustards were first investigated in England[1-4] reports of their use in the treatment of blood diseases came first from America[5-7] and later from this country.[8] Two aliphatic compounds of this series, HN2 or methyl-*bis* (β chloroethyl) amine hydrochloride and HN3 or *tris* (β chloroethyl) amine hydrochloride, have been used extensively in the palliative treatment of Hodgkin's disease and allied conditions. In this issue of the *Journal* Dr. J. D. N. Nabarro reports on the use of the *bis* derivative in a small number of patients over a period of three years. He found that when the glandular masses were localized radiotherapy gave better results than nitrogen mustard. On the other hand, cases in which the disease is widespread from the beginning respond better to nitrogen mustard than to radiation. Occasionally in the terminal stages of the disease a dramatic remission may occur after the administration of nitrogen mustard. Recently an aromatic nitrogen mustard, *bis* (β chloroethyl) β naphthylamine, has also been tested in the treatment of Hodgkin's disease and other conditions.[9] This last compound has some advantages over the aliphatic chloroethylamines, since it is much less toxic, can be administered orally, and does not cause the nausea and vomiting which almost invariably accompany treatment with HN2 or HN3.

The value of these substances in the treatment of cancer is still difficult to assess, but they appear to have a definite place in the palliative treatment of lymphadenopathies. In other forms of malignant disease their action is much less certain: the results obtained in most cases of cancer arising other than in lymphoid tissue and the lungs have not been encouraging. Symptomatic improvement has followed the administration of HN2 in a proportion of cases of carcinoma of the lung. Rhoads[10] was probably the first to describe a case of this kind; he studied the effects of nitrogen mustard on various types of neoplastic tissue and observed a remarkable temporary remission in a patient with anaplastic carcinoma of the lung. Out of forty-one patients with lung carcinoma treated with HN2 at the Royal Cancer Hospital[11] by Boyland and his colleagues about one half obtained symptomatic relief and showed objective signs of improvement. In these the pain, cough, dyspnoea, and general malaise were relieved, and decreases in caval obstruction, in the amount of sputum and pleural exudate,

1 Boyland, E., *Brit. J. Pharmacol.*, 1946, **1**, 247.
2 Dixon, M., and Needham, D. M., *Nature, Lond.*, 1946, **158**, 432.
3 Hanby, W. E., Hartley, G. S., Powell, E. O., and Rydon, H. N., *J. chem. Soc.*, 1947, 519.
4 Hanby, W. E., and Rydon, H. N., *J. chem. Soc.*, 1947, 514.
5 Goodman, L. S., Wintrobe, M. M., Dameshek, W., Goodman, M. S., Gilman, A., and McLennan, M. T., *J. Amer. med. Ass.*, 1946, **132**, 126.
6 Karnofsky, D. A., Burchenal, J. H., Ormsbee, R. A., Cornman, I., and Rhoads, C. P., *Approaches to Tumor Chemotherapy*, 1947, Washington, p. 293.
7 Spurr, C. L., Jacobson, L. O., Smith, T. R., and Barron, E. S. G., ibid., p. 306.
8 ApThomas, M. I. R., and Cullumbine, H., *Lancet*, 1947, **1**, 899.
9 Annual Report of the British Empire Cancer Campaign, 1948, p. 59.
10 *J. Amer. med. Ass.*, 1946, **131**, 656.
11 *Brit. J. Cancer*, 1948, **2**, 17.
12 *Glasg. med. J.*, 1949, **30**, 197.
13 Karnofsky, D. A., Abelmann, W. H., Craver, L. F., and Burchenal, J. H., *Cancer*, 1948, **1**, 634.
14 *Brit. J. Cancer*, 1949, **3**, 118.

and in the size of metastases were observed. Some patients increased in weight during treatment, and in others there was radiological evidence of improvement, with some remission of physical signs in the chest. The remissions which occurred were only temporary, lasting from two weeks to three months. Although no serious adverse reactions were noted the authors considered that nitrogen mustard does not greatly advance the treatment of carcinoma of the lung. It may prolong life in some cases, though this is difficult to assess, and it sometimes relieves distressing symptoms and thus may make the patient's remaining days more tolerable. Very similar results have been obtained by Brown and Davis in Glasgow[12] and by American workers[13]; the latter consider that nitrogen mustard may be more effective and less hazardous than radiotherapy in cases with rapidly growing anaplastic lung cancer.

That the chloroethylamines have a demonstrable clinical effect on bronchogenic carcinoma in man has been established, but it has not been possible so far to show that they have a corresponding effect on other types of carcinoma. This probably indicates some specificity of action on certain tissues. It must be remembered, however, that patients are acutely conscious of symptoms arising from disease of the lungs and of variations in their severity. In bronchogenic carcinoma a slight diminution in the size of a tumour or in the amount of tissue reaction around it may be sufficient to afford notable relief from the distressing symptoms. This apparent specificity of the nitrogen mustards is analogous to that of oestrogens in cancer of the prostate and breast and of urethane in leukaemia. These two substances are also carcinogenic: oestrogens induce mammary cancer and urethane induces cancer of the lung in mice. Boyland and Horning[14] have recently shown that the aliphatic nitrogen mustards can induce carcinoma of the lung, sarcomas, and lymphosarcomas in mice. The aromatic nitrogen mustards have induced cancer in rats. Thus the nitrogen mustards resemble the oestrogens and urethane in that they themselves are carcinogenic. Though the effects obtained with these agents are comparable, the mechanism of their action is unknown. Better understanding of this may lead to the discovery of drugs of greater practical importance than the nitrogen mustards.

[12] *Brit. J. soc. Med.*, 1948, **2**, 106.
[13] The Registrar-General's Decennial Supplement, England and Wales, 1931. Part IIa. *Occupational Mortality*, 1938. London: H.M.S.O.

SEX DIFFERENCES IN MORTALITY

A difference between the death rates of males and females has been a feature of the vital statistics of England and Wales since registration was introduced in 1836. The advantage possessed by the females over the males for all ages combined has not always appeared in the various age groups. One hundred years ago the females had a higher death rate than males at ages 10–20 and 25–45. The rate of decline in the death rates in the last decades of the nineteenth century varied in different age groups, but generally the fall was greater among females than among males. The only exceptions were at ages 5–9 and 10–14, and at the beginning of the present century the females had a higher death rate at these ages than the males. It was commonly thought that working conditions were partly responsible for the higher death rate among men during adult life. In the past 50 years, however, conditions of work have improved considerably; shorter hours are worked, and the gross industrial toxic risks have been eliminated. As a consequence of the improved standard of living the male death rate has fallen rapidly, but curiously enough the female death rate has fallen even more rapidly. At the present time the death rate of women is lower than that of men in each age group, though of course the fatality rate of some diseases is higher among women than among men. Perhaps the best-known exception to the general trend is the higher death rate from whooping-cough among female than among male children.

It has been suggested that the different social habits of males and females may in part explain the difference in the mortality rates, and this is possibly true for those diseases in which alcohol worsens the prognosis. One of the many interesting permanent features of the vital statistics of England and Wales is that the ratio of the death rate in rural areas to that of the general population is proportionately lower for males than for females. Most of the explanations put forward to explain this and other differences are too speculative to be satisfactory.

The latest inquiry into this problem is that of Johnstone and Hosker,[1] who took the Registrar-General's supplement on occupational mortality[2] as their main source of information and compared the experience of males, single women, and married women. With the exception of appendicitis every disease which causes a higher mortality among men than among women also causes a higher mortality among single women than among married women. In married women the death rates from cancer of the uterus and, after the age of 45, from diabetes are higher than in single women, but married women have a lower mortality from bronchitis, pneumonia, tuberculosis, peptic ulcer, cancer of the breast, and pernicious anaemia. They also commit suicide less often than single women. Differences between the death rates of men and women similar to those in England and Wales occur in other countries: for instance, adult females have a higher mortality from diabetes than adult males in the U.S.A., Canada, and New Zealand; and in girls under 15 years of age in these countries the death rate from whooping-cough is higher than in boys. Johnstone and Hosker conclude that occupational differences must be one of the important reasons for the dissimilarity of male and female death rates.

TOXIC FACTOR IN BLEACHED FLOUR

Not quite three years ago Sir Edward Mellanby's first report[1] on the experimental production of canine hysteria was published in the *Journal*. Hysteria was produced in dogs and subsequently in ferrets[2] by feeding them with flour treated with agene (nitrogen trichloride), the flour improver and bleacher which has been in common use in this country and in the U.S.A. for the past twenty-five years. Later work on agene-treated flour fully confirmed

[1] *British Medical Journal*, 1946, **2**, 885.
[2] Ibid., 1947, **2**, 288.
[3] Ibid., 1948, **1**, 350.
[4] Ibid., 1948, **1**, 843.
[5] Bentley, McDermott, Pace, Whitehead, and Moran, *Nature*, 1949, **163**, 675.
[6] Butler and Mills. *Nature*, 1949, **163**, 835.
[7] Bentley, McDermott, Pace, Whitehead, and Moran, *Nature*, 1949, **164**, 438.

Mellanby's conclusions and was discussed at the time in these columns.[3] These confirmatory studies led the Food and Drug Administration of the United States Government to prohibit the use of agene, a prohibition which came into force as recently as August 1.

It was subsequently pointed out by British and American workers that the toxic agent was formed from the protein of the wheat and particularly from the gliadin fraction.[4] Since Mellanby's first observations on the subject there has been increasing interest in the identity of the toxic substance responsible. A great deal of work has been carried out by Moran and his co-workers[5] at the Cereals Research Station of the Research Association of British Flour Millers and also by other workers.[6] This has now been rewarded by the isolation at St. Albans of a crystalline substance which either is or contains the toxic factor.[7] The crystals are of needle-like appearance, melt sharply with decomposition at a temperature of 232° C. (uncorrected), and their biological activity is unaffected by further recrystallization. As in previous work, the maize protein, zein, has been used as the starting-point. In the normal way it would be said that this crystalline isolate was a pure substance, and that it only remained to establish its composition and chemical identity. But the indications are that it will prove to be a peptide; and with peptides, as with proteins, there has been a recent reminder that apparently "pure" and homogeneous crystals may turn out to be mixtures of different substances. None the less, this is an important advance, and the further progress of this work will be awaited with interest.

POLIOMYELITIS VIRUSES

The Fourth International Neurological Congress which has just ended its meetings in Paris was remarkable for a number of important and interesting communications. The discussion on virus infections of the central nervous system was of topical interest. The production of allergic encephalomyelitis and the relation of this condition to post-vaccinial encephalitis and to paralytic rabies on the one hand and on the other hand to disseminated sclerosis were the subject of a number of papers. The epidemiology of insect-born encephalitides was reviewed and a number of cases of recurrent benign meningitis were described; whether this condition is due to a virus or to allergy is still undecided. New strains of rabies virus with reduced neuronotropy have been investigated and may be of value for rabies immunization.

Perhaps the most important discussion, however, was on poliomyelitis. It was suggested that in backward countries the acquirement of virucidal bodies to the Lansing strain of poliomyelitis without overt signs of infection may result from prolonged breast-feeding whereby immune bodies are passively transferred from mother to child; the young child thus passively immunized acquires an active infection as a result of the prevalent defective sanitary conditions. The new phenomenon of virus exaltation in relation to poliomyelitis viruses was also described: doubtless more will be heard of this condition, which is the reverse of virus interference.

Few of the neurologists attending the Congress had yet realized that what is now described as poliomyelitis is a symptom complex produced by at least three distinct groups of viruses. The term poliomyelitis in fact must now be used only in a general sense, much in the same way that typhus is used to describe broadly a number of distinct infections due to different species of rickettsiae. Historic or classical poliomyelitis includes the group of viruses isolated from human faeces, nasal washings, or spinal cords. It is not a uniform group, but consists of at least four varieties which are antigenically distinct. The first of these is the Lansing type, which has been transmitted from man to monkeys and thence to cotton rats and mice. Six of these rodent-adapted strains are known, and have been isolated from patients in the Middle East and America, while virucidal bodies to these viruses have been found in Europe, America, Asia, and Africa. Three other antigenically distinct strains of true poliomyelitis virus are recognized, and there may be others, since not all material from patients dying with poliomyelitis yields positive results on inoculation into monkeys.

The second group of viruses all showing antigenic similarities and capable of producing paralysis in man comprises the Mengo encephalitis virus from Uganda, the EMC (encephalomyocarditis) virus isolated from a monkey in California, and the MM and Columbia SK viruses, which were probably derived from rodents. One of this Columbia SK group of viruses may have been responsible for an outbreak of poliomyelitis in American troops in the South West Pacific area. This group of viruses is transmissible to man, monkeys, and rodents such as mice and hamsters. These viruses can be inoculated by a variety of routes, including intramuscular injection, and they are pantropic, producing lesions in organs other than the central nervous system. Immune bodies to this virus are widely distributed.

The third group of viruses isolated in America is transmissible only to suckling mice or hamsters; distinct antigenic varieties occur, and there is now evidence that these viruses exist in Western Europe. It must be emphasized that these three groups of poliomyelitis viruses are quite distinct from the mouse encephalomyelitis viruses, often incorrectly termed "mouse poliomyelitis," which are transmissible only to mice and hamsters. Such viruses have been isolated from mice in America and in Britain. The virus infection of pigs which attacks the anterior horn cells of the cord is also distinct from human strains.

It is thus obvious that certain views on poliomyelitis will have to be revised. Some work is already in progress here on the newer aspects of poliomyelitis, but, as it now appears probable that recurrent epidemics will visit this country at frequent intervals, it is essential that a comprehensive attack should be made on these problems.

TONOSCILLOGRAPHY IN PERIPHERAL VASCULAR DISEASE

Nomenclature is an ever-increasing burden to the medical profession, and to many the term tonoscillography may seem just one more weighty straw. In this word the prefix "ton" (from τόνος, meaning tension) indicates that the height of the blood pressure is obtained simultaneously with the size of the arterial pulsations from the written record of an oscillogram. Ejrup,[1] of Stockholm, has broken entirely new ground by applying the results of

tonoscillography after exercise to problems connected with the diagnosis, prognosis, and treatment of vascular disorders of the extremities. If his findings are confirmed and his technique found not too time-consuming for general application in less expert hands than his own the early diagnosis of these conditions and the assessment of their severity should become much easier.

The idea of simultaneous automatic recording of blood pressure and arterial pulsation is not new,[2-5] but Ejrup's apparatus is both original and simple. It consists of two cuff-pressure systems actuated independently by automatic valves which inflate or deflate the cuffs at accurately controlled pressures and time intervals. The cuff applied to the proximal part of the limb to be studied—the pressure cuff—is connected to a manometer which by means of a lever inscribes a record on a continuous recording strip. The lower or pulse cuff is lightly distended at a fixed pressure, and small volume variations of arterial pulsations are recorded electrically with a movable pen attached to the same lever as the pressure cuff while the latter is steadily inflated. Diastolic pressure is recorded at the point where the form of the pulsations suddenly alters, and the point where all pulsation ceases indicates the systolic pressure. Automatic recordings are taken in this manner every 20 seconds—venous congestion being avoided by complete emptying of the cuffs in the intervals. Strict precautions are of course necessary in order to obtain comparable records. Although systolic end-points are clear, diastolic pressure is by no means always obvious in the published records.

By employing Nylin's[6] standard exercise step-tests Ejrup found that a raised blood pressure and increase in pulse amplitude in the legs invariably occurred immediately after exercise in healthy subjects. Records after exercise were remarkably constant in the same individual on different occasions, in contrast to resting records, which showed considerable variations. In patients with organic arterial obstruction, on the other hand, whether due to Buerger's disease, arteriosclerosis, or embolism, a characteristic inverse response was obtained: there was a decrease or even absence of all pulsations after exercise and a lowering of the pressure at which pulsations disappeared—i.e., an apparent lowering of the systolic pressure. In 10 cases in which the site of obstruction was determined by arteriography the level on the leg at which the inverse reaction appeared could be predicted with precision by the tonoscillograph. All but two of the 54 cases of intermittent claudication showed an inverse response, and patients with unilateral symptoms always gave a bilateral inverse response, more pronounced in the painful leg. A similar inverse reaction was also found to occur in aortic coarctation, in which, as is well known, arterial pulsation in the legs is diminished. Some of the 17 patients in this series complained of claudication, but a typical inverse response after exercise was found in every case. Treatment by the Crafoord resection operation resulted in the disappearance of the inverse reaction, and normal responses were obtained.

Ejrup's method of study of obstructive arterial disease of the extremities gives objective information which cannot be obtained by the more usual and comparatively cruder methods of oscillography. The new technique appears to make possible the accurate and early diagnosis of obstructive arterial lesions in the limbs and precise location of the site of the obstruction. It can provide confirmatory evidence of coarctation of the aorta, and it may perhaps prove valuable in determining the presence of other causes of obstruction to aortic flow, or of lesser degrees of narrowing of the aortic isthmus, in the cases in which other investigations give equivocal results and in which the femoral pulse is easily felt. The latter type of abnormality is probably more often missed than detected, particularly when associated with patency of the ductus arteriosus.[7] Ejrup claims that his method of tonoscillography is of value in differentiating functional disorders of the limbs from those due to obstructive arterial lesions, and that it can also be used to measure the extent of remission or progression of disease following treatment (of which many forms have been advocated) for arterial disorders of the extremities. Confirmation of his findings will be awaited with interest.

FUNCTIONAL VENTRICULAR FIBRILLATION

Arrhythmias originating in the ventricle, apart from isolated or short sequences of extrasystoles, are usually an expression of serious ischaemic heart disease, and are much more rarely encountered with an apparently normal heart than the corresponding disorders in the auricle. Ventricular fibrillation is, indeed, most often a terminal event, or, if survived, is an indication that the patient has not long to live. An unusual, perhaps unique, case has recently been reported by Moe,[1] who was able to record attacks of ventricular fibrillation in a man of 38 in whom no evidence whatever of organic heart disease could be discovered. After a period during which he noted palpitation the patient had a number of syncopal attacks, and a cardiogram obtained during one of these showed ventricular fibrillation lasting for 18 seconds, the patient being unconscious, the pulse impalpable, and respiration stopped. Before the fibrillation solitary extrasystoles and groups of extrasystoles were recorded, and after it a bradycardia, probably due to A-V nodal rhythm. A record on the following day showed normal rhythm with flat T waves, but on the second day these had become normal. Ten syncopal attacks were observed in one day, the number probably being augmented by treatment with injections of adrenaline; this was given on the supposition that the attacks were due to heart block. After appropriate treatment with quinidine the attacks soon ceased and have not recurred, except on one occasion when the quinidine was temporarily discontinued. Short runs of ventricular extrasystoles are the only arrhythmia which has since been recorded, and the patient remains well taking 0.1 g. of quinidine daily. Clinical and *x*-ray examination has failed to reveal any sign of organic heart disease. If Moe's interpretation of this case is correct, the possibility of functional ventricular fibrillation appears to be established.

[1] *Amer. Heart J.*, 1948, **35**, 41.
[2] Bergman, A., *C. R. Soc. Biol., Paris*, 1922, **87**, 1046.
[3] Fidhlom, E., *Acta med. scand.*, 1936, **88**, 45.
[4] Stockvis, von B., *Cardiologia, Basel*, 1940, **4**, 75.
[5] Weiss, H., *J. Lab. clin. Med.*, 1941, **26**, 1351.
[6] Nylin, G., *Z. klin. Med.*, 1931, **118**, 584.
[7] Gilchrist, A. R., *Brit. Heart J.*, 1945, **7**, 1.

[1] *Acta med. scand.*, 1948, **130**, 416.

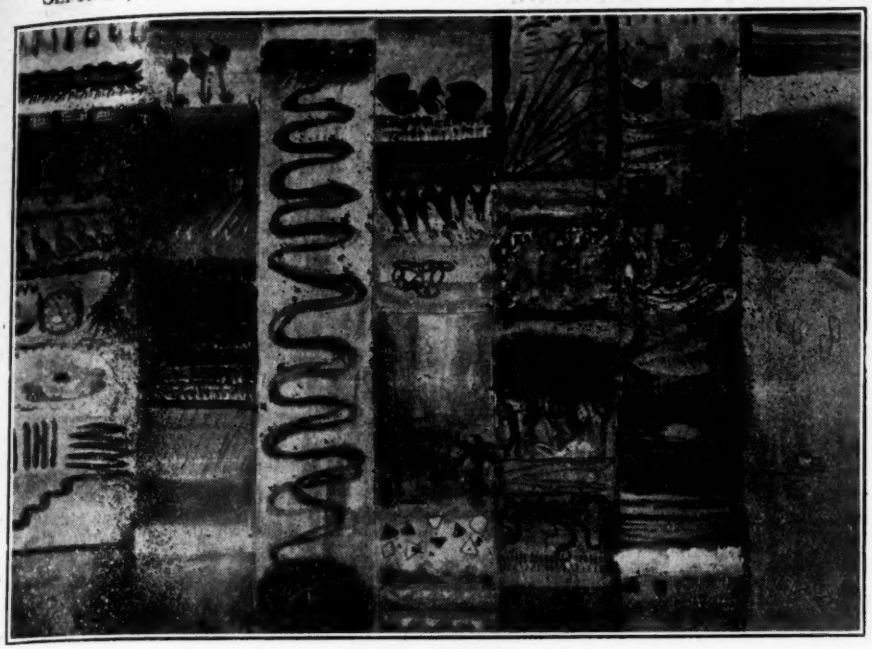

FIG. 1.—A Week.

THE PATIENT WITH THE PAINT-BRUSH

EXHIBITION OF PAINTING

An exhibition of paintings by patients from the Mental Treatment Centre, Hill End Hospital, St. Albans, was opened by Mr. Victor Pasmore at Trefoile House on September 7. The exhibition contains over 50 pictures that have been painted since the previous display 18 months ago. Most of these are the efforts of people who have painted only during a few months' stay in hospital and have never used a paint-brush before.

The paintings differ widely in character. Some are frankly objective, others are more obviously a means of emotional release. Yet each represents a form of personal creativeness and is stamped with the individuality of the painter. The artist's work is something into which his personality enters and through which his imagination finds release, which establishes painting as a useful adjunct to standard psychotherapy.

The exhibition shows also the latent powers of artistic expression possessed by those who make no pretence to special talent. Mr. Pasmore emphasized that these paintings had been executed for enjoyment and not for the purpose of analysis, and he observed that the gallery strongly resembled an exhibition of children's art. This, he said, indicated the fallacy of the opinion that fresh artistic creation was impossible after early youth.

The pictures reproduced here represent three of the different styles seen at the exhibition. "A Week" is a patient's impression in paint of seven days in his life while in hospital. "The Ravine" and "Autumn Tapestry" are imaginative studies in contrasting design.

Mr. N. C. Colquhoun and Dr. W. J. T. Kimber, medical director of the hospital, were in charge of the painting class. The exhibition is open between 9 a.m. and 6 p.m. and will continue until October 1.

Photographs of the paintings by *Sport and General*.

FIG. 2.—Autumn Tapestry.

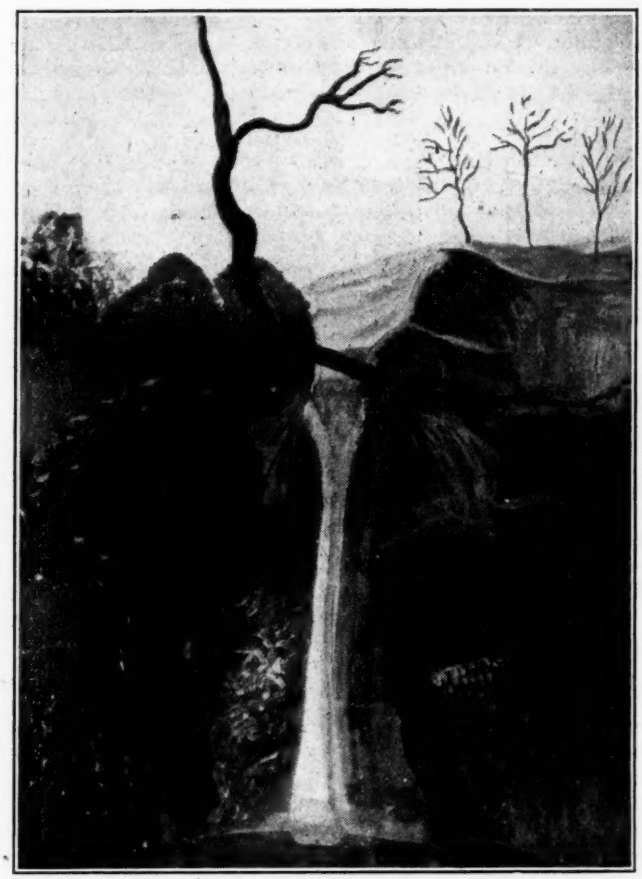

FIG. 3.—The Ravine.

BRITISH ASSOCIATION

MEETING AT NEWCASTLE-UPON-TYNE

The 112th annual meeting of the British Association was held at Newcastle-upon-Tyne from August 31 to September 7, and was the fourth largest meeting in the association's history.

The presidential address on world population and world food supplies, given by Sir John Russell, formerly director of the Rothamsted Experimental Station, was commented on in a leading article in the last issue of the *Journal* (p. 585). Sir John Russell concluded that "the increased food production that may be confidently expected is more than ample for population increases at Western rates," but that "it could easily be outstripped locally where Eastern rates of increase prevail."

Sir John referred also to the induction of lactation in cows by diethylstilboestrol as the first stage in making the male redundant, and discussed the possibilities suggested in livestock breeding by the combination of artificial insemination and transplantation of ova. Edwards has estimated that by suitable dilutions the number of inseminations from one bull could rise to 10,000 or even 15,000 per annum. J. Hammond, jun., and Bhattacharya at Cambridge have shown that a cow injected with pregnant mare serum will produce a number of ova per oestrum instead of one, and attempts are now being made to transplant these into other cows, one into each, fertilize them by artificial insemination, and so get a dozen or so offspring from the chosen mother. One cow so treated might produce 75,000 ova in her lifetime, and scrub cows, otherwise of little use, might be employed as her incubators.

The Cell

The presidential address in the section of physiology was given by Professor R. A. Peters (Oxford). He discussed the cell from the point of view of the biochemist, beginning with a reminder that the development of British anti-lewisite, now available as an antidote to certain antimony and mercury compounds, as well as arsenicals, had originated in the application of a rational biochemical approach to the problem of arsenical poisoning. Like iodoacetic acid—which occupies an important position in the historical development of biochemistry—the arsenicals act by blocking a particular stage in the chain of enzyme-activated conversions which leads from glycogen to lactic acid. Such a block should lead to the accumulation of the last preceding substance. This has not been demonstrated *in vivo* in iodoacetic acid poisoning. But in the case of arsenical poisoning the accumulation of pyruvic acid has been shown *in vivo* as well as *in vitro*, thus providing a bridge between the laboratory schemes worked out by biochemists and what takes place in the human body. The participation of thiamin in the co-enzyme needed in the same stage of the glycogen–lactic acid sequence has also been demonstrated. A further such "bridge" is in the accumulation of citrate *in vivo* in fluoroacetic acid poisoning, as required in the current cyclic scheme of changes postulated to explain the oxidation of the "two-carbon" fragments formed in the metabolism of carbohydrate and fat. Such bridges are important because of—to quote Sherrington—the "mush of unrecognizably disintegrated cells" from which biochemists start their preparations; but Professor Peters added: "The onus is no longer on us if this biochemistry is not taken seriously."

Proceeding to the properties of the cell as a whole, Professor Peters recalled, first, that chemical reactions which required different conditions must be capable of proceeding simultaneously (the "microkitchen" argument); secondly, that the heart cell could respond as a whole to an amount of acetylcholine which would cover only one-six-thousandth part of its surface; and, thirdly, that the substance of the cell could be thought of as a jelly, which in essence was a fluid. He could not picture the reaction of the cell as a whole to a single local stimulus on the basis of "bags" of enzymes floating in a protoplasm which was itself without structure, and such reactions did not become intelligible until he took the view that the cell was organized as a whole. The benzene ring reacted as a whole, and its organization as a whole enabled properties to be interpreted which would be otherwise unintelligible; and so he believed it would be with the living cell.

Finally, he referred to the individuality of the cell as suggested by the failure of skin grafts, even from near relatives. Such failures, he suggested, appear to be explicable only by taking the view that there is some protein constituent in the skin graft which is different for every individual. The identification of genes with enzymes he thought uncertain; and as regards cell division and growth, it seemed a better approach to tackle first the non-dividing cell.

In the discussion, to which Professor Peters's address served as the introduction, Dr. R. Barer (Oxford) described the advantages of new methods of microscopy in relation to cell structure. The phase-contrast microscope enabled the intact living cell to be studied under improved conditions, and the reflecting microscope allowed absorption measurements to be made in the ultra-violet and infra-red regions with no change of focus. He demonstrated electron-micrographs obtained by Draper and Hodge,[1] showing the localization of minerals in skeletal muscle. The essential features were the combination of long filaments running lengthwise, with extremely fine transverse striations and wider transverse bands. Professor A. C. Frazer (Birmingham) referred to possible molecular arrangements of lipoproteins which could be concerned in cell structure, and Dr. E. N. Willmer (Cambridge) spoke on "the cell from the aspect of tissue culture."

Microbial Digestion

A discussion on microbial digestion in the alimentary tract was held jointly by the sections of physiology and agriculture. It was introduced by Dr. D. P. Cuthbertson, director of the Rowett Research Institute, Aberdeen. He said that, since all mammals so far examined had a microbial population in the large intestine, this form of digestion must be general and normal. In carnivores, such as the wolf, fermentation on any large scale did not take place, but in most other mammals the caecum and colon had the size and the environment suitable for bacterial growth. Only substances produced outside the living microbial cell, or made soluble by autolysis of the dead cell in the large intestine, were made available to the host. In the ruminant the rumen and reticulum, the first two of the four compartments of the stomach, formed a large fermentation vat where coarse fodder material, indigestible to the non-ruminant, could be rendered available to the organism and new compounds of importance to the animal could be synthesized.

Dr. S. K. Kon (Reading) discussed the microbial synthesis of vitamins of the B complex and of vitamin K. This had been shown to take place in the intestinal tract of most avian and mammalian species, but in ruminants occurred also in the rumen, so that conditions for utilization were specially favourable. Studies with animals having permanent fistulas into the rumen showed that the rumen contents were substantially richer on a dry-weight basis than was the original diet. This applied to almost all the vitamins of the B complex which had been measured. The young ruminant, however, was without this active microbial flora during the first few weeks of life, and was as dependent on an external supply of vitamins as the dog or the rat.

American investigators had compared the input and output of different vitamins in healthy adults receiving diets deficient in one or more of these factors. The average faecal excretion of all the vitamins studied was as high on the restricted as on the normal diet, so that there must have been appreciable synthesis; but average urinary output was lower, thus illustrating the point that the value to the host of such synthesis was limited by intestinal absorption. On the other hand, an interesting condition, that of refection, could arise when certain non-ruminants received a diet rich in raw starch. In this condition animals normally dependent on a supply of vitamins in the food could dispense with it entirely. The occurrence of refection in the rat was dependent on the presence of raw starch and of starch-splitting organisms in the caecum. The animal became a vicarious ruminant, the caecum combining some of the functions of the rumen and the true stomach.

[1] *Nature*, 1949, **163**, 576.

Dr. J. Tosic (Rowett Institute) mentioned the ability of micro-organisms found in the rumen to assimilate cobalt and other trace elements from their external environment, and discussed the connexion of this with possible mechanisms of cobalt and other trace element deficiencies in the ruminant.

Pernicious Anaemia

Discussion of microbial digestion led into a further discussion on folic acid, vitamin B_{12}, and anaemia. Vitamin B_{12} is the first pure substance of biological origin in which cobalt is contained.

Dr. E. Lester Smith (London) stated that knowledge of the absorption by ruminants of vitamin B_{12}, probably made by bacteria, had come to light through work on the need of chicks and other animals for a factor present in animal but not in vegetable proteins. It was then found that this factor could be synthesized by certain bacteria, and about the same time it became clear that it was none other than vitamin B_{12}. One organism that made useful amounts was *Streptomyces griseus*, already in commercial use for streptomycin production, and crystalline vitamine B_{12} has already been isolated from this source.

Dr. C. C. Ungley (Newcastle) distinguished between the megaloblastic anaemias according to the presence or absence of gastric atrophy. In Addisonian pernicious anaemia the effects of vitamin B_{12}, given by various routes and with and without gastric juices, suggested that it permitted the detoxication of the haemolytic factor. Vitamin B_{12} was also as effective as liver extract in the treatment of the neurological changes. Pteroylglutamic acid (folic acid), on the other hand, was only temporarily or partially effective. But in the second group, without gastric atrophy, pteroylglutamic acid was effective in small doses, and vitamin B_{12} even in large doses was either ineffective or only partially effective.

Planes of Nutrition

Planes of nutrition in livestock were discussed in the section of agriculture in relation to shortages of feeding-stuffs and the economic return, measured by the conversion of one foodstuff into another. Mr. R. W. Pomeroy (Cambridge) spoke of sheep and pigs. In sheep, a low plane of nutrition during early pregnancy had no effect on the size of the foetus, but a high plane during late pregnancy made it more likely that the lamb could be sold as a "fat lamb" direct from the ewe. Such a combination therefore gave the greatest return from available extra feeding-stuffs. In pigs, with more numerous progeny, the problem arose of the feeding of the young pigs as well as of the sow. Young pigs benefited most from a high plane of nutrition up to 100 lb. (45 kg.) live weight; less from a high plane of nutrition thereafter. The most efficient conversion of foodstuffs was through a high plane of nutrition followed by a low, and the difference compared with the reverse procedure was as much as 70%. Sows usually proceeded without intermission from lactation to pregnancy, and a high plane of nutrition was needed for recovery from lactation. With less certainty, it was argued that a high plane of nutrition during late pregnancy was undesirable, on the grounds that excessive lactation was promoted and also a clumsiness of movement which could be dangerous to the young pigs.

Dr. S. Bartlett spoke of dairy cattle. He suggested that cows, cowmen, and examination candidates were all of the opinion that there was only one way of feeding dairy cattle, and that was as laid down in official publications. There were discrepancies between British and American figures for extra milk yield; but if farmers could be induced to supply extra food, and cows to eat it, an adequate physiological response should be obtained.

In the section of physiology Dr. R. Passmore (Edinburgh) summarized the results of a dietary survey of 298 students under 21 years of age which had been carried out by the Department of Public Health and Social Medicine of the University and the Scientific Advisers' Divisions of the Ministry of Food.[1] The minority of students on an ill-balanced diet were evenly distributed among both sexes and among those living at home and in lodgings, the diets of those living in university hostels being on the whole well-balanced. From interviews with students it was concluded that even at university level there was a real need for elementary health education, ignorance being more important than lack of money in determining bad feeding.

[1] A. H. Kitchin, R. Passmore, M. Pyke, and G. M. Warnock, *Brit. J. soc. Med.*, 1949, 3, 10.

Psychology and Industry

Sir Godfrey Thomson's presidential address to the section of psychology consisted of a criticism, on the ground of method, of the tendency to multiply mental factors. His general attitude was that factors of different sorts were useful and vivid additions to the psychologist's vocabulary, but that "they are not at all unitary and only partially innate, being built up in the individual mind by many external influences." Probably the general level of intelligence owed most to heredity—a "ceiling" which the individual might fail to reach but could not surpass. With other so-called mental factors, Sir Godfrey suggested that much more was due to environment.

A discussion on human problems in the design of machinery and working methods was opened by Dr. N. H. Mackworth (Cambridge). Dr. G. B. Frisby (National Institute of Industrial Psychology), who followed, argued that satisfaction in work should be regarded as a basic requirement. A machine limited by its design the freedom of action of the worker, and so did methods of manufacture, even in assembly and other manual work. Lay-out, special jigs, and tools all determined that the job should be done in one way decided not by the worker but by the production engineer. This favoured the "we—they" attitude. The size and complexity of the individual task were also reduced, and the tendency had been to accept as inevitable both this increased subdivision and the reduced satisfaction that went with it. There was a need for research on the nature of the satisfactions which could be felt from work. For example, could pride in skill persist where the creative element had disappeared? In any event, if the production engineer proceeded in his breakdown of jobs beyond the point at which loss of satisfaction occurred for the majority of his workers, then efficiency would decline. Speed, shown by the stopwatch, might increase, but persistence might fall, and labour wastage and absenteeism might increase.

Piltdown Man

The status of the Piltdown skull, found by Mr. Charles Dawson a few miles north of Lewes in 1908, seems to have been finally settled by two communications to the section of anthropology. Dr. K. P. Oakley (British Museum) presented the results of the fluorine test by which the age of bones found in the same geological sequence can be roughly compared. Skull and jaw had proved approximately contemporary—thus settling one argument which has persisted even to the present year—but neither was likely to be older at most than 100,000 years. There could be no question, therefore, that Piltdown Man and, say, Pekin Man could be approximate contemporaries.

Dr. Robert Broom (South Africa) reported in a written communication that he had independently reached the conclusion that the Piltdown jawbone belonged to the same individual as the brain case; that this was a big-brained type of man which evolved on a quite different line from true *Homo*; and that the "simian shelf" in the lower jaw was probably an indication of parallel evolution rather than of close affinity with the anthropoids.

THE LISTER INSTITUTE

Macbeth exclaimed, "Bring me no more reports; let them fly all," and in the office of a medical journal it is difficult not to sympathize with him. Of some reports it can be said that their copiousness is in inverse proportion to the importance of what they describe; but of others that their volume is as meagre as the work itself is outstanding. The latter is true of the annual report of the governing body of the Lister Institute of Preventive Medicine for 1949. This is a thin pamphlet of 13 pages and describes the year's work of a staff of about 50 highly skilled research workers, all engaged on special lines of study. The report is so short that the work done at Chelsea

Bridge Road remains largely uninterpreted, even to the expert engaged on a parallel line of research. It is true that most of the work is a continuing study—that is to say, reportable results are not necessarily forthcoming in a particular year—but the pursuit should be worth reporting as well as the goal. To name only a few of the lines of research which are proceeding makes their potential importance evident.

Work is being carried out on the factors concerned in the virulence of *Haemophilus pertussis* for mice, and the influence of such factors on the immunizing properties of whooping-cough vaccines; on methods of preserving vaccinia virus without the use of refrigeration; on precipitating antisera against the blood of man and animals with the object of identifying blood meals of blood-sucking insects; on the haemolysis of erythrocytes from different species of animals by clostridium toxins; on the nature of the linkages in gramicidin most susceptible to acid hydrolysis; on the examination electrophoretically of a group of sera from cases of pneumoconiosis; on factors in blood clotting; on the metabolism of nicotinamide and related compounds as affected by diet—and on many other lines of investigation in the bacteriological, biochemical, biophysical, and nutritional fields.

Some of the nutritional studies are interesting. One of them is on the effect of vitamin A on gastric conditions. Cases of peptic ulceration, or of gastric pain without ulceration, treated with vitamin A as out-patients at the Royal Free Hospital have been followed up. Healing of the ulcer has been demonstrated radiographically in some cases. Continuous treatment for six to ten weeks seemed the most satisfactory, and prolongation of continuous treatment for long periods caused relapse in a few cases. Sometimes, after an interval of six to twelve months after treatment, pain would return, and another course of six weeks' treatment was then necessary. Cases studied at the Medical Branch of the General Post Office at Mount Pleasant have also been followed up, and the results confirmed those obtained at the Royal Free Hospital. Vitamin A has been studied further in relation to the stomach of rats. Search has been made for the factor which prevents proliferation of the gastric epithelium when the animals are deprived of this vitamin. Efforts to find the factor in casein prepared in various ways have proved unsuccessful, and recourse has been made to certain vitamin-A-deficient flour diets. Flour of 85% extraction has been used, and in a preliminary experiment with 18 rats epithelial proliferation, though not entirely absent, was very much less than with any other diet tried. It did not appear to be of significance whether the flour was bleached or unbleached.

The Blood Products Research Unit of the Institute has issued during the year large quantities of dried human plasma and plasma fractions for clinical use, also 2,500 ampoules of gamma globulin for clinical trial in cases of measles.

It is announced that Lord Horder, owing to the increasing demands on his time, has resigned his seat on the governing body after fourteen years' service. Dr. A. N. Drury has been appointed in his stead. The governing body again records its appreciation of the continued co-operation and collaboration of the Medical Research Council, the work of whose external scientific staff is described in the report.

DRUG ADDICTION IN BRITAIN

REPORT TO THE UNITED NATIONS

The British Government's Report[1] for 1948 to the United Nations on the traffic in opium and other dangerous drugs was published last week. Approximately 395 addicts are known to the Home Office—198 men and 197 women. Of these, 112 are doctors, 3 dentists, 1 a veterinary surgeon, and 3 pharmacists. Information about addicts is generally obtained by Home Office inspectors and by the police in the course of normal routine inspections of the registers kept by wholesale and retail chemists, and by visits to doctors who are prescribing for patients who are addicts. All the addicts are reported to have obtained their supplies from legitimate sources—i.e., on prescription. During the year eight doctors were convicted of violation of the narcotic laws, and in six of the cases the authority to possess, supply, and prescribe dangerous drugs was withdrawn by the Secretary of State. Eighteen men and six women were reported as having been cured of their addiction during the year; eleven of these were doctors. Approximately 12% of all the addicts are reported to be using pethidine either alone or together with another drug.

The only regular illicit importation of dangerous drugs to this country is carried on by merchant seamen, who are usually Chinese, Indian, or African. The drugs they bring in—mostly Indian hemp and opium—are used almost entirely by themselves or by their fellow countrymen. This illicit traffic is largely confined to the seaport towns, but during the year three negroes were arrested in Birmingham for being in unlawful possession of Indian hemp. It was discovered that they had obtained their supplies in Liverpool, where three other men engaged in trafficking were arrested. There was only one case during the year in which drugs from legitimate sources were suspected of having been diverted into the illicit traffic. In this case two men, both addicts, were proved to have forged certificates showing that accomplices of theirs were registered as drug addicts abroad. The accomplices were then introduced to two doctors in London who, because of the forged certificates, were induced to prescribe heroin and cocaine.

Supervision is exercised by Home Office inspectors over persons authorized to possess and use dangerous drugs. Inspection of retail pharmacists is carried out as a matter of routine by the police forces throughout the country. The inspectors, who advise and assist the police in this work, also visit retail pharmacists either casually or in the course of special inquiries. Doctors' records of dangerous drugs may be inspected by regional medical officers, who are ready to give advice on cases of addiction. If a doctor, dentist, pharmacist, or veterinary surgeon has been convicted of irregularities connected with the supply of dangerous drugs the Secretary of State is empowered to deprive the offender of his authority to possess, supply, or prescribe the drugs.

During the year pethidine and amidone were added to the list of drugs for which a separate register or part of a register must be kept. No modifications in the administrative arrangements for implementing the information convention were made during the period.

[1] *The Traffic in Opium and Other Dangerous Drugs.* Report to the United Nations by His Majesty's Government in the United Kingdom of Great Britain and Northern Ireland for 1948.

Nova et Vetera

THE PITCAIRNS

Three Pitcairns have acquired places in medical history—Archibald (1652–1713), William (1711–91), and David (1749–1809). David was the nephew of William, and William was of the family of Archibald, although what William's precise relationship to Archibald was, Munk does not say. Archibald Pitcairn, according to Munk, was "celebrated as the founder of the mechanical sect of medicine." This is hardly accurate: Borelli (1608–79) came before him. Borelli, however, was not much of a physician, and Haeser assigns to Archibald Pitcairn the honour, if it is an honour, of carrying the application of iatro-mechanical physiology in practical medicine to its highest point. Haeser gives Alexander Pitcairn a page and a half, but had probably formed the opinion—certain to be entertained by a modern reader—that iatro-mechanism was rather silly. He permits himself to say that Pitcairn, "like all one-sided theorists," was apt to swear by empirical remedies, and instanced the human skull and earthworms as part of Archibald Pitcairn's pharmacopoeia. It is, humanly speaking, certain that neither William nor David Pitcairn ever prescribed either, but William had great faith in opium and there is a story that his nephew David, when a medical student in Edinburgh, saved the life of Professor William Cullen's son by conveying his uncle's advice to administer laudanum freely.

Haeser has nothing to say of William and David Pitcairn, neither of whom published anything; both kept such theories

as they had to themselves. William Pitcairn prescribed opium freely, but David seems to have had little faith in drugs. Of him it is said that when a young physician commented on the inertness of his prescription in a case of consumption he replied: "The last thing a physician learns, in the course of his experience, is to know when to do nothing, but quietly to wait and allow nature and time to have fair play in checking the progress of disease and gradually restoring the strength and health of the patient." Not so terse as Hippocrates, but Hippocratic.

Uncle and nephew were esteemed by the public and their colleagues. William Pitcairn was president of the Royal College of Physicians for ten years, 1775–85, and retired from practice in 1784, when he was appointed treasurer of St. Bartholomew's Hospital. He was physician to the hospital for 30 years (1750–80). His nephew David followed very closely in his steps; he was elected physician to St. Bartholomew's in 1780. If Munk's dates are right there seems an irregularity in the hospital's practice, because in 1780 David Pitcairn was neither M.D. (he graduated M.B.Cambridge in 1779 and M.D. in 1784) nor a licentiate of the College—he was admitted candidate in 1784 and Fellow in 1785. It is possible that, as his uncle was president, the College did not enforce its legal rights.

David Pitcairn followed his uncle as physician to Bart's within a week, and might well, after a somewhat longer interval, have succeeded him as president of the College had not his health failed in his fiftieth year. Residence for 18 months in Portugal was followed by improvement, and on his return to England David Pitcairn partly resumed work, but his health was broken and he died in 1809, two years younger than his uncle was when first elected president of the College.

As the judicious reader will have noted, Munk, whom I have followed, could add little to what was so well said in *The Gold-headed Cane*, and Macmichael (1784–1839) was a very young man when David Pitcairn died. The only estimates by contemporaries which survive are the eloges of deceased Fellows, then pronounced not by presidents but Harveian orators and not in English but in Latin (in not very good Latin, according to a better judge than I am). But an elogist is likely to dwell on good traits. Cadogan emphasized William Pitcairn's kindness to his professional colleagues, Heberden (the younger) David Pitcairn's excellence as a clinical teacher and his kindness to hospital patients. Great teachers are as rare as great investigators and inevitably fill less space in medical histories. Trousseau is mentioned by the learned Haeser only as a French physician influenced by German medicine, but any reader of his *Clinique Médicale* (1861) can understand why he impressed medical students. David may be the greatest of the three Pitcairns, because a tradition established by a fine teacher outlives him and still works for good when he is forgotten.

Heberden co-ordinated the treatment of the poor and the power of the teacher in his eloge of David Pitcairn (pauperes pene innumerabiles cura sublevavit, multosque discipulos, praeceptis ex re natis, ad medicinam faciendam optime instituit). Another great Bart's teacher, Peter Mere Latham (1789–1875), was in the succession. Latham and Trousseau, in eloquent words which have survived, impressed on their pupils the importance of *humanitas*, which, like *honestas*, means so much more than the English derivative. The Bob Sawyers of a century ago needed that lesson more than their great-great-grandchildren. Callousness and brutality in students are no longer to be feared. But in an age of gadgets and official forms, when "case" and "patient" are used as synonyms, it may still be worth while for the young physician to borrow a friend's—or his grandfather's—"Lewis and Short" and look up *humanitas*.

MAJOR GREENWOOD.

The Pharmaceutical Society of Great Britain was represented at the Assembly of the International Pharmaceutical Federation in Amsterdam in August by the President, Mr. H. Clement Shaw, Professor Brindle, Professor Todd, Dr. J. M. Rowson (who read a paper at the Assembly), Mr. E. A. Brocklehurst, Miss M. A. Burr, Mr. J. F. McNeal, and Mr. H. N. Linstead (joint secretary). Mr. F. W. Adams (joint secretary and registrar) accompanied the delegation.

Correspondence

Distinction Awards

SIR,—While I am wholly out of sympathy with the theme and spirit of Dr. H. E. A. Boldero's letter (September 10, p. 594), yet I can still congratulate him upon having packed into its short space more sophistries than I should have thought possible save in an election address.

All the usual rationalizations of the temperamentally acquiescent appear there in their tawdry unreality. The proposition that because a national health service is a desideratum, therefore all that is now happening is "the wish of the people," whereas, as everyone knows, it represents nothing more than a Cabinet policy; the implication that, save for a few unpractical reactionaries, the entire profession is hastening to help and guide "the Government of the day" (how familiar the phrase is to Fellows of the Royal College of Physicians); and, worst of all, the sinister reminder to young consultants that unless they go quietly they will, financially speaking, have their necks wrung like chickens. "Bow to the inevitable, there is a cheque behind it" is in effect Dr. Boldero's stirring appeal to youth.

Against this too familiar pattern there rises to meet our ears the orchestra of complaints and lamentations against the working of the Health Service that echoes loud in every issue of the *Journal*, coming from every professional group save—so far—the graded consultants. The body of general practitioners festers with resentments, and the graded hospital officers have grievances not less bitter. To this cacophony there will surely be added in due time the complaints of those consultants who are dissatisfied with their "distinction" gradings, and if these go underground and are not heard in the medical press they will be none the less deeply felt and will destroy the harmony of medical staffs. All this is very different from Dr. Boldero's pleasant fantasy of a profession striving almost unanimously to help the Government to perfect the manifestly imperfectible. Surely if things were as Dr. Boldero would have us believe we should be piping more tunefully and with a better grace.

It is possible that I am in a minority amongst my fellow consultants on this issue, for the power of money is great; but I believe that the only real distinction now left to the consultant is to be of this select minority and to remain *hors concours* in the competition for State subsidies.

If consulting practice as we have known it at its best is to die, it will not be because of the fears of the younger men but because the old men who should have foreseen and averted their painful dilemma lacked vision and the spirit of courageous leadership. To be acquiescent in the drift towards the helotry that faces us is not, *pace* Dr. Boldero, to be constructive. And to bow to the inevitable—that we have made such by bowing to it—is not the high spot of heroic virtue. At least, we did not think so in 1940.—I am, etc.,

London, W.1. F. M. R. WALSHE.

Co-operation with Institutes of Education

SIR,—In your educational number Professor W. R. Niblett (September 3, p. 526) urges co-operation between institutes of education and medical schools, and you comment favourably on this suggestion in a leading article. I should like to endorse the great value of such co-operation. Soon after the start of the Institute of Child Health at the Hospital for Sick Children, Great Ormond Street, in 1946, contact was made with the Director of the Institute of Education of the University of London. Soon afterwards a standing joint committee was formed to deal with matters of mutual interest. There is a free interchange of staff for teaching purposes, and the Child Care Training and Research Scheme at the Foundling Hospital site is a joint effort of the two bodies. Moreover, the Institute of Education has organized a series of conferences on teaching methods for the staff of the Institute of Child Health, when selected speakers opened discussions on such subjects as the use of the lecture, the value of tutorials, visual aids, and voice production, which were extremely helpful. The need

for collaboration with an institute of education is perhaps more obvious for a school or department dealing with children than for those covering the older age range. I am certain, however, from our own happy experience that Professor Niblett's advice should be widely followed. It is perhaps immodest to add that the fruitfulness of the collaboration is not, I think, one-sided.—I am, etc.,

Institute of Child Health, University of London. ALAN MONCRIEFF.

Essential Hypertension in Pregnancy

SIR,—Mr. R. H. Paramore writes (August 27, p. 486) that he is not satisfied with the statement made by Mr. John Sophian (August 6, p. 335) in the sense that vascular spasm is the primary change inducing hypertension and that it is the cause of renal cortical ischaemia.

To this concept Mr. Paramore opposes his hypothesis that anuria, whether in the pregnant woman or not, is not the result of a decreased intrarenal blood flow, but on the contrary that it is due to an increased blood flow to the renal medulla, which maintains the "obstruction" of the uriniferous tubules. He attributes to the reduction of the medullary blood flow the benefits derived from repeated spinal anaesthesia, which he so wisely advocated more than twenty years ago. He is probably right in this, but perhaps not in the sense that he thinks it to be.

In favour of his views he mentions Clifford White's histological findings in renal tubules which were obtained from "a minute piece of the kidney" (in White's words) from two uraemic patients; indirectly, he also seems to value the fact that he did not find "any reference to the effect of the secretion of urine on the blood flow through the kidney" in the book *Studies of the Renal Circulation*, in which I was a collaborator. He considers this omission of fundamental importance. While I hope to contribute soon to the discussion of these and other related problems in a more extensive manner, I must now advance that on p. 36 of the English edition of our book there appears a reference to our observations on the correlation between a diminished urine flow and a diminished cortical circulation.

As our immediate purpose was to study the renal circulation and not the renal function we were for the moment satisfied with the confirmation of the findings made more than a century ago by Claude Bernard, who showed that the electric stimulation of the splanchnic nerves caused the urine flow to decrease or even to cease, an observation which has been untiringly repeated since then. We also dispose of a copious mass of information about the renal vascular response to this and other types of stimulus, such as certain hormones (adrenaline, "pituitrin," "pitressin"), toxins from staphylococci, streptococci, and *B. welchii*, and even to simple oxygen lack. The effect of all these apparently different vascular stimuli is to cause constriction of intrarenal vessels. If the stimulus is sufficiently powerful it might cause total renal ischaemia, whereas if the stimulus is of a moderate nature it might only cause a reduction of the calibre of the more excitable intrarenal vessels, such as those of that part of the cortex which is not anastomosed with either perirenal or medullary vessels. It is a consequence of the cortical arterial constriction that the medullary vessels appear engorged in some cases of fatal anuria. In others the whole of the kidney suffers from anoxia.

As a surgeon who has had for many years the misfortune of being confronted with serious forms of traumatic and surgical shock I have difficulty in understanding how shock might help in increasing urine flow. Up till now kidney failure in shock has been one of the greatest surgical problems. We know through a series of careful clinical and experimental observations that "primary" or immediate shock is characterized by renal vascular spasm (see among many others the papers from the school of van Slyke). Probably this vascular spasm is beneficial, as it reduces both the circulatory area of the vitally non-essential organs and it also helps to maintain the blood volume by stopping urine formation.

After a certain time the renal anoxia caused by vascular spasm gives way to that of peripheral collapse of "secondary" shock. In this later stage urine flow is interrupted, not by a functional and reversible mechanism such as arteriolar spasm, but by damage to that part of the kidney which is more sensitive to the lack of oxygen—that is, the tubular cells. I cannot understand how high spinal anaesthesia may contribute to the flow of urine otherwise than by releasing the arteriolar constriction. This seems to be the mechanism of the kidney which "obstructs" the flow of urine. Mr. Paramore gave an early answer to this most pressing necessity by advocating the method which in its more elaborate modern form has in the hands of Dr. Robert A. Hingson produced such satisfying results.—I am, etc.,

Oxford. J. TRUETA.

Medical Education

SIR,—Having read the series of articles in your educational number (September 3) I feel that consideration has been directed in the main too much towards the route and too little towards the destination. The ultimate aim must be the production of a general medical practitioner, yet this point certainly was not emphasized in your *Journal*. Specialization follows after qualification.

Are we in danger of forgetting this? It would appear that we are, since more and more time is being asked for and undue importance attached to the subsidiary clinical subjects. Instead of their being separate entities they should be fused and administered under the general headings of medicine, surgery, obstetrics and gynaecology, and pathology. For example, place paediatrics under medicine, despite the recent development of professorial chairs in paediatrics. Maternity and child welfare and venereal diseases would come under obstetrics and gynaecology, and haematology would assume its rightful place in the more general subject, pathology. These few examples may irritate specialists in the subjects mentioned, but they serve to illustrate the point I wish to make, that with integration would come realization of sphere of influence. And the time has come for specialists in certain subjects to realize that in their subject the requirements for the medical student may be generalizations rather than minutiae. A director of clinical studies would go far to make fusion and administration less difficult.

Professor W. Melville Arnott (p. 497) fears that the increased number of students may result in large ward classes. This need not be so if a considerable part of the present wastage of clinical material is utilized. The greater the number in the class often means the more competitive the spirit in that class. The area union of hospitals should make this problem easy of solution provided the universities are willing to pay their teachers a rate of salary comparable to that in the National Health Service and thus attract sufficient numbers. So far as lecturing is concerned, to lecture to a few is most discouraging. I had the privilege recently of attending a lecture to a class of 250 students of obstetrics in Sydney, Australia. There Professor Bruce Mayes has a microphone installed in his lecture room! The 250 were the survivors from a class of nearly 600 that had started the course. Yet I was assured that each student delivered more than thirty obstetric cases him- or herself—a triumph for administration and utilization of available material.

Let us unite, even at the sacrifice of personal pride in the importance of one's subject, to integrate the subjects in the curriculum so that we produce in the end a man or woman trained in the essentials for general practice. In the words of *The Times* (August 27), "If general practice is not raised to a new level of competence—some would say, restored to its rightful place—the whole of British medicine will suffer."—I am, etc.,

Oxford. G. GORDON LENNON.

Postgraduate Education of General Practitioner

SIR,—The new academic year is approaching and in consequence much is being heard of undergraduate education. I feel it is also an opportune moment for something to be said about the postgraduate education of the general practitioner. If the general practitioner is to play his part in modern medicine it is essential that he should be able to maintain his contact with

its rapid advance. Much lip service is paid to his importance, but I feel that too little attention is given to the means which would enable him to justify that importance. Fortnightly or week-end courses, which appear to be the main suggestions to this end, can never be effective; they are liable to provide the practitioner with a mass of information of which at the best he could absorb a little and which at the worst would only confuse him further.

There are, to my mind, two possible answers to this problem. First, the long-term answer, the integration of the general practitioner with the local hospital. This, though a formidable problem, is not impossible and might bring advantages from the patient's point of view. Secondly, short five-working-day periods of attachment to a moderate-sized hospital where each day men of the standing of clinical tutors could teach for a period of three hours on selected cases. I feel that three hours' teaching is as much as most people can use without boredom. The rest of the day the practitioner could partake in the work of the hospital, much as do junior housemen and clerks. The advantage of the five-day period is that few men could not spare this once or twice a year.

In a further effort to enable the general practitioner to keep up to date I would like to suggest that, at periods appropriate to the advances in the subject, monographs similar to that on sulphonamides published by H.M. Stationery Office should be made available. Unless one is conversant with the particular specialty, articles such as are printed in the various journals cannot be evaluated by the practitioner. I feel that the monograph should not be by an individual, who may have a personal bias, but by a committee, who could state the present body of fact and belief on which the bulk of practice must be based.

This, as behoves a letter, is merely in the form of a suggestion which will I hope stimulate our teachers to consider what can be done to help the general practitioner to fill adequately his place in the new medicine which is before us.—I am, etc.,

Blackburn, Lancs. FRANK LIVESEY.

Training in Public Health

SIR,—I read with interest your leading article (September 3, p. 523) on training in public health. It is indeed encouraging to note that you have such confidence in the future of the public health service—a view which is shared by few at present engaged in preventive medicine.

I believe there to be a great future in public health, but with this assumption—namely, that the preventive approach will be introduced more and more into the medical curriculum. In this connexion much of the D.P.H. course could usefully be taught to undergraduates. If this were so our colleagues in the curative branches of medicine would not only have some sympathy towards our motives but would give us their active co-operation. When all doctors have instilled into them the importance of social and environmental factors in the causation of disease, and when we can all work together in health centres, I see no reason why G.P.s and specialists alike should not constantly seek the advice of the M.O.H. on the social and environmental problems of their patients. The M.O.H. could then indeed become a "true specialist in preventive medicine."

This brings me to an extract from your article: "Financially the rewards of a career in public health will always be less than clinical medicine can offer." Why? Is it not somewhat illogical to state categorically that the financial rewards of preventive work must always be less than those for curative work? Must prevention take second place to cure? Would not the only just solution to the salaries question be to take the three main branches of the profession—general practice, public health, and specialist—and give them a common minimum and a common maximum and work out a salary structure in each within the same limits? The newly qualified doctor could then choose his career according to his inclinations without being biased by financial interest.

The opportunities in public health are infinite—one can only hope they will be grasped with both hands. The first round of the public health battle, that against epidemic infectious disease, has to a great extent been won. Now we can turn our energy against the social and environmental factors in the aetiology of other forms of disease. Shall we move along these lines? I hope so, but I believe the bias of medical education will be the deciding factor.—I am, etc.,

Chester. B. G. GRETTON-WATSON.

Goethe, an Appreciation

SIR,—Another great admirer of Goethe's *Faust*, I have been surprised to see that none of those who recently contributed in expressing their love of this unique work quoted the scene from Part I which has a direct bearing on medicine and which would have fitted so well into your educational number. Having pulled the scholar's leg mercilessly over the choice between logic, metaphysics, and law, Mephistopheles continues as follows (in Bayard Taylor's translation):

"To grasp the spirit of Medicine is easy:
Learn of the great and little world your fill,
To let it go at last, so please ye,
Just as God will!
In vain that through the realms of science you may drift;
Each one learns only—just what learn he can:
Yet he who grasps the moment's gift,
He is the proper man.
Well made you are, 'tis not to be denied,
The rest a bold address will win you;
If you but in yourself confide,
At once confide all others in you.
To lead the women, learn the special feeling!
Their everlasting aches and groans,
In thousand tones,
Have all one source, one mode of healing;
And if your acts are half discreet,
You'll always have them at your feet.
A title first must draw and interest them,
And show that yours all other arts exceeds;
Then, as a greeting, you are free to touch and test them,
While, thus to do, for years another pleads.
You press and count the pulse's dances,
And then, with burning sidelong glances,
You clasp the swelling hips, to see
If tightly laced her corset be.
Student: That's better now! The how and where one sees.
Mephistopheles: My worthy friend, grey are all theories,
And green alone Life's golden tree."

Has anyone ever poked better fun at our respected brotherhood? And as to Part II, I entirely agree with Mr. H. Corsi (September 3, p. 546): it is by no means inferior to Part I. The scene which precedes Dr. Corsi's second quotation (Act 2, i), where the Student returns and proves himself very much a match for the Devil, will hold its significance for all generations of teachers and pupils. Altogether it is nearly impossible to get through a day's events without wanting to quote from *Faust* again and again. Rarely has profound wisdom been expressed in such beautiful language.—I am, etc.,

Pinner, Middlesex. E. ELKAN.

Poliomyelitis and Social Environment

SIR,—The careful study of poliomyelitis and the social environment by Professor A. Bradford Hill and Dr. W. J. Martin (August 13, p. 357) must have had a salutary effect on a number of observers who, like myself, were of the opinion that there was a relationship between the two. No one could question their results, but at the same time they have dealt with one side of a question which would appear to have two different aspects.

To quote from their own conclusion: "According to this experience favourable mortality rates indicating the favourable social conditions of a locality need not raise fears of an unduly heavy risk when poliomyelitis becomes widespread." The possibility that poliomyelitis is related to social environment might also be considered from the point of view of incidence among social class rather than incidence in an environment which contains all social classes, and my own experience, which

I realize to be very limited, has been to associate the disease with a favourable social grading.

I find on discussion with colleagues that they also feel that there is a social class distribution in relation to poliomyelitis which is quite different from that of other infectious diseases, and I would like to suggest that a second survey to prove or disprove this contention should be conducted. Simply with the idea of stimulating interest in this direction I gathered case histories of twenty-one consecutive cases which have come under my observation and placed them into social classes according to the occupation of the principal wage earner of the family. The result was as follows: Class 1, 3 cases; Class 2, 5 cases; Class 3, 7 cases; Class 4, 4 cases; and Class 5, no cases. The remaining two were a student at a primary school training college and an infant in a county council children's home.

If the above suggestion was supported by an observation on a sample of sufficient size to permit of statistically accurate deductions being made it would provide interesting material for speculation. Apart from complex associations which might be brought forward, there is a simple fact that during the period when poliomyelitis is epidemic there is a much greater amount of travel among families with larger incomes. This in turn could be an effective factor in either of two directions. In the first place it could be an application of the conclusion reached by Ritchie Russell[1] on the effect of prolonged fatigue as a predisposing factor. In the second place it could help to explain the peculiar way in which cases occur during an epidemic. These generally start with foci in a few areas and are followed by sporadic cases in many different areas.

If more accurate social histories were taken from all cases occurring during an epidemic year and the lines of travel of the affected persons in widely separated areas in the country correlated, it might be found that the apparent sporadic occurrence of cases was to a large extent mythical, and that explosive outbreaks are occurring—the cause being disseminated by victims who are passing through a long and symptomless incubation period. This would surely present a more reasonable picture of a disease which reaches its height in the middle of a hot, dry summer and is practically unknown in January.—I am, etc.,

Brill, Bucks. V. O. B. GARTSIDE.

REFERENCE

1 *British Medical Journal*, 1947, **2**, 1023.

Streptomycin in Infantile Gastro-enteritis

SIR,—In your annotation entitled "Streptomycin in Infantile Gastro-enteritis" (August 27, p. 478) you refer to an article of ours (*Lancet*, 1948, **2**, 555) and say we found "that oral streptomycin alone was effective whether or not other foci of infection were present. . . ."

In fact, our experiences were quite the reverse. In discussing case 18 we said: ". . . The recurrence of diarrhoea and vomiting was due to the parenteral infection, and this should have been recognized and treated before streptomycin was considered. In the presence of such an infection streptomycin by mouth is valueless." Again, in the summary we wrote: "The administration of streptomycin by mouth does not obviate the necessity of treating parenteral infection, which may play a part in the causation of gastro-enteritis." We consider this so important that it is worth while drawing your attention to the error in the annotation.—We are, etc.,

URSULA JAMES.
IVOR R. H. KRAMER.

London, S.W.3.

Vitamin E

SIR,—I have just read your account (May 28, p. 951) of the International Conference on Vitamin E held recently in New York, as well as the annotation on vitamin E in the same issue (p. 949). As the person who first noted that α-tocopherol had a definitely beneficial effect on certain types of heart disease, diabetes (independently of Butturini, whose observations antedated mine by four years), and arterial peripheral vascular lesions I might be able to contribute something to the general principles underlying the use of this vitamin in these conditions.

In the first place, it is a common error to assume that vitamin E is used in these conditions as a form of replacement therapy or to remedy a deficiency. I believe that these conditions do not result from vitamin-E deficiency and that the vitamin is used as a chemical substance (in much larger doses than are needed to raise blood levels to normal) to obtain a specific physiologic effect. This can be supported by the observation that 20 mg. per day of *d*-α-tocopherol acetate will raise the blood tocopherol level to normal (about 1 mg. per 100 ml.), whereas for a therapeutic effect in the previously mentioned conditions it is necessary to give initial doses of 200 to 600 mg. daily for several weeks. The dosage may then be reduced, but in most cases at least 200 mg. per day will be required indefinitely as a maintenance dose.

Unfortunately, all of the papers which I have read by authors who had noted no satisfactory results have failed to use the method which I have suggested. I have yet to hear from any physician who has followed this method and has been disappointed in his results. It must be noted that in patients with heart disease who require digitalis the digitalis must be continued after the vitamin E is begun, but at somewhat lower doses than ordinarily used. I would certainly appreciate hearing from any British physician who might try this method.—I am, etc.,

281, Oxford Street, London, Ontario. A. VOGELSANG.

Cortisone

SIR,—In 1933, while doing clinical research which sought to show the existence of a tuberculous diathesis based on over-activity of the lactogenic principle of the pituitary gland—producing what I believed was tantamount to a culture medium for the tubercle bacillus, consisting of excess releasable lipin-protein in all cells at times other than the puerperium—I decided to test the action of suprarenal gland extract as a possible pituitary depressant in this respect in a case of pulmonary tuberculosis. The suprarenal extract used was in the ordinary tablet form supplied by Burroughs Wellcome and Co.

Six days after administration had commenced, the patient, a man of 25 years and of the stoutish, smooth-skinned type, exhibited all the classical signs of rheumatic fever. The treatment was stopped, and with the introduction of salicylates all the signs of rheumatic fever disappeared within ten days. Although the use of the suprarenal extract came under suspicion as an exciting factor in this flare-up, that suspicion was not strong enough to prevent a further test. But on its readministration all the signs of rheumatic fever recurred; they again subsided quickly on its withdrawal, and without the assistance of salicylates. The conclusion had to be that a suprarenal secretion, probably in excess, could be a cause of rheumatic fever, and, for the purposes of my theorizing, that its action on the pituitary was an exciting rather than a depressing one. Further experience suggests that stilboestrol, had it then been available, was the substance I was seeking for my purpose, as was suggested in my paper, "Early Pregnancy and Epitheliomata," published in the *British Medical Journal* (1924, **2**, 1149). Stilboestrol will depress the pituitary.

I have always favoured a theory that the rheumatic fever and tuberculous diatheses were related in a way which could perhaps be explained graphically, as is done in the case of organic compounds by the addition or removal of side chains; and that whereas rheumatic fever and pulmonary tuberculous diatheses were dependent on a pituitary-stimulated over-supply to all cells of a basal vital food product (a lipin protein) at all times, and not confined to the female only—as at times of full mammary activity—certain forms of arthritis, on the other hand, were the result of a deficiency in this same product. It seemed, therefore, that suprarenal gland extract would be of value in cases of menopausal arthritis, and I tried it in three cases of this disease in 1937, but with only a suggestion of an improvement. It is clear now that the extract was not sufficiently refined.

I think the above facts ought to be reported, because, of course, the use of 17-hydroxy-11-dehydrocorticosterone or "cortisone" in rheumatoid arthritis appeals to me as a discovery that will bring real results, but also strongly because

my own findings suggest avenues for research into the cause of rheumatic fever as well as the treatment of tuberculosis. My efforts also seem to point to a real danger if this new substance, once it becomes available, is used anything like as empirically by medical men generally as were the sulphonamides and penicillin.—I am, etc.,

St. Annes-on-Sea, Lancs. C. W. A. EMERY.

Foreign Body in the Stomach

SIR,—The following may be of interest as suggesting a new technique in the extraction of foreign bodies from the stomach without operation. I have not come across anything in the medical press up to now embodying a similar experience.

A boy aged 9 years swallowed an aluminium and enamel bottle top about the diameter of a halfpenny or rather less. It remained in the stomach for a week in spite of efforts to coax it through the pylorus by a skilful radiologist. I therefore decided to remove it, as I feared, possibly erroneously, that it might cause symptoms of aluminium chloride poisoning. Under general anaesthesia I made a small left paramedian incision and located the foreign body in the stomach. I caught up an avascular area between two tissue forceps and isolated the area with gauze swabs. On incising the stomach and seeking the foreign body with a pair of sponge-holders I failed to locate it. I then explored the stomach from cardia to pylorus with my forefinger and again failed to locate the object. To my astonishment the pylorus was dilated to the size of a florin and patulous. On picking up the stomach wall with the tissue forceps I must have shot the foreign body through this dilated pylorus as through the neck of a sack. I then found that as soon as I had opened the abdomen my anaesthetist had given a dose of curare to give as much relaxation as possible, as I was working through a small incision. The bottle top was duly recovered by the natural route 48 hours later.

I assume that all this came about through the complete relaxation under curare, and that a similar result may possibly be achieved in other cases of the same kind without the necessity of open operation.—I am, etc.,

Plymouth. C. F. MAYNE.

Hypnosis in Treatment

SIR,—You have done the ordinary non-specialist doctor a service in publishing articles on hypnosis at this time when everybody seems to be aware of it and interested in it, gleaning information either from articles in journals or from witnessing stunt displays of hypnosis in music halls. The doubt which exists in some of our minds is concerned with the question, Is it safe ?

It is agreed that the central phenomenon is that of dissociation, in which I suggest it is the higher intellectual and critical faculties which are in abeyance and suppressed. The mind is then influenced on the feeling level and to a lesser degree on the intellectual level by the hypnotist : in effect we may say that the hypnotized subject is to a great extent depersonalized.

There are many of us who believe the individual personality to be sacrosanct on philosophical, ethical, religious, or moral grounds, and we attempt in our doubtless ignorant way to support and strengthen the personalities of those anxiety-type patients who consult us, so that they can have some objective view of their difficulties and overcome them themselves with our help rather than surrendering their personalities to a hypnotist, however skilled he may be and however high his motives.

I agree that there are conditions of hysteria where hypnosis is useful and valuable, as in battle conversion hysterias. But I feel that before hypnosis becomes more widespread there should be an inquiry into its effects on the whole personality, including its potentialities, by psychologists, general practitioners, religious leaders of several denominations, and philosophers.

The last war has shown us how some individuals with the most aware and most integrated personalities were able to face and overcome the severest tribulations without depersonalizing themselves. Pain is always enhanced by fear, especially when the fear is long sustained and not attached to immediate and obvious objective reality. I believe that dissociation is effective in producing an anaesthesia of the sense of fear rather than a resolution of it; the enemy is avoided rather than defeated.

Modern medical science permits marked relief from physical pain without having to resort to hypnotism. Under hypnotism the subject is depersonalized and behaves in a manner which has little relevance to what is generally judged on empirical grounds to be objective reality and which may be to a large extent inappropriate to his situation. This is done by the voluntary surrender of the higher functions of the mind to another person, with evidence of feelings of relief from tension, or of satisfaction.

An occasional pleasing experience of this sort may easily become a routine habit, with the result that the personality never faces and overcomes a problem but becomes anaesthetic to it, and thereby is likely to be weakened by this practice in the long run. I hope that the experts will be able to reassure us.—I am, etc.,

Birmingham. K. M. HAY.

The Value of Drugs

SIR,—On glancing through "Any Questions ?" (August 6, p. 345) my attention was arrested by a categorical and presumably authoritative denial of the rationale of administering vitamin A and D as a general prophylactic against infection.

While keeping an open mind on the subject, it does seem to me that the simple bald statement in reply raises an enormous question that affects the whole of medicine and could hardly be dealt with in the limited space of your columns. It is simply this : With the exception of recognized specific remedies, how many of the various mixtures and preparations in common use can be definitely shown to have a positive and beneficial effect on the patient ? Many of my more cynical colleagues, I fear, would be inclined to answer that question in one word.

It does seem that when so much difficulty is experienced in assessing the therapeutic value of new methods of treatment many of the "mixtures" and "tonics" that we are forced to prescribe would show up very poorly under the searchlight of modern scientific investigation. If it were possible to know the verdict of such investigations on the value of more popular mixtures and drugs we could at least have the satisfaction of knowing that even though we deceive our patients we do not deceive ourselves.—I am, etc.,

Bristol. J. E. G. HOPE SCOTT.

Syringes

SIR,—While the doctor in a single practice must admire the care and efficiency of the syringe service described by Dr. T. G. Benjamin (July 30, p. 282), he will be unable to adapt the system economically or satisfactorily for his own use.

For nearly two years I have been using one firm's portable water-boiling syringe sterilizer. It consists of a metal case with bakelite surround. The lid, on removal, carries with it a cylindrical metal cage divided into four sections. Three sections can hold syringes (or, incidentally, small instruments). The fourth is adapted to take six needles, well protected and separated from each other. The whole is contrived so that the syringe can be selected and assembled very rapidly without the hand touching anything but the barrel. A flex with universal plug allows the sterilizer to be boiled from any average lamp or wall socket. Finally the whole fits into a small transporting case with a carrying handle.

I use two of these sterilizers: one remains at my place of work and the other comes on rounds. This last is sterilized at home. As soon as it has boiled sufficiently the lid with the cage is lifted clear and the sterilizer emptied. The remaining steam quickly dissipates and the lid and cage are replaced, leaving practically dry syringes and needles ready to be used when required. If necessary (and this is rare) the sterilizer can be refilled with water and boiled up again very quickly in the patient's home.

In the sterilizer I carry two syringes of 2 ml. and one of 5 ml. capacity, which covers almost all everyday requirements. Needles of different sizes are set up in routine positions so that the required size can be selected at once. Though this does not fulfil the ideal of the M.R.C. recommendations for dry sterilization and individual packings, it is a very good second best, and a great time-saver and convenience.

Finally, I should be interested to follow Dr. Douglas Gairdner's advice on Luer syringes (July 30, p. 282), but a supplier tells me that these are becoming increasingly difficult

to obtain and that an order for Luer-fitting needles may take six months to fulfil. I am well content with the metal-topped and glass-pistoned Record syringe.—I am, etc.,

Cambridge. A. S. PLAYFAIR.

SIR,—Dr. Douglas Gairdner (July 30, p. 282) and Mr. John Foster (August 13, p. 387) may be interested to know that hypodermic syringes with nozzles of the Luer type have already been standardized for use in this country. They form the subject of B.S.1263, which was issued in 1946. Agreement on this standard was reached by a technical committee representative of the various using, manufacturing, and other interests concerned, who felt that the Luer nozzle presented advantages over other nozzles, including the Record type.

It was realized at the time that the change over to this standard syringe could only be gradual and would take some little while. The Record type of syringe has been used extensively in the past, and in consequence it was realized that there would be a continuing demand for replacements of needles until the syringes themselves were replaced.

It is, however, somewhat disappointing that there should still be such a large demand for supplies of the Record needles, as the production of needles to fit the Luer type of syringe is thereby being prejudiced. It was confidently hoped that with the support of the Ministry of Health for the adoption of syringes with the Luer nozzle the change over would be more quickly effected, as it is obviously in the interests of all concerned that those syringes with the much more satisfactory type of nozzle should come into use as quickly as possible.

Manufacturers of needles and syringes are ready to meet all demands made on them incorporating the B.S.1263 or Luer nozzle fitting, and it now only rests with the hospitals and other users to make their contribution by adopting syringes with the Luer nozzle as soon as they can.—I am, etc.,

S. J. EVERETT,

Thornton Heath, Surrey. Chairman of B.S.I. Committee on Syringes.

Gravitational Ulcers of the Leg

SIR,—Dr. S. T. Anning (August 27, p. 458) rightly stresses the role of the deep veins in the causation of gravitational ulcer. Deep thrombosis is a factor in a far higher proportion of patients than is generally realized. I do, however, join issue with him on one most important point, when he states that the treatment of superficial varicose veins in patients with venous stasis is neither rational nor useful, and more often than not harmful.

Unfortunately this is still widely taught, but I believe it to be entirely incorrect and based on the strange misconception that the superficial varicose veins aid the circulation by acting as collateral vessels to the blocked deep veins. On the contrary, in varicose veins of the kind under consideration the blood flow in the erect position is almost invariably downwards. This can be easily demonstrated. When this is so the veins are no asset, but a liability in every way.

One is sometimes asked how in these circumstances the blood returns from the lower limb. The answer is, of course, that there are not two, but three, interconnected systems of veins. For convenience one may refer to them as the deep, the varicose, and the unnamed. With the deep veins thrombosed, and the varicose veins taking the blood the wrong way, there must be a third system to do the work. These unnamed veins are the key to the situation; they comprise veins within and between the muscles, sometimes segments and duplications of deep veins which have not been affected by the thrombosis, and such subcutaneous veins as are still competent. Most of them are small, but their total blood capacity is considerable. They carry upwards not only the blood brought to the limb by the arteries but—and this is the essential point—also that which flows back into the limb via the incompetent varicose veins. This is the basis for ligating varicose veins in cases of deep venous thrombosis. It cannot be other than beneficial if the flow in them is downwards. How beneficial it will be depends on what proportion of the load on the unnamed veins is due to the venous reflux. This is difficult to assess before operation. One has to be prepared for little obvious improvement, but in the majority of cases the improvement is striking. A complete cure in so far as the patient's symptoms and healing of the ulcer are concerned (which means that the unnamed veins are now capable of carrying the load) is exceptional. Even with the help of other treatment, especially the support which is advisable in nearly all cases, real cure is unusual. One has to face this and so has the patient.

Ligation never makes the venous stasis worse; it can and should be done regardless of the state of the deep veins. Many authors avoid committing themselves on this point. Their remarks often take the form of an injunction to use discretion in advising operation for patients with a history of thrombosis. The reader, seeking guidance, too often does not get it. Aware of the danger of oversimplification, I am convinced that the indication for ligation is simply retrograde flow of blood in the vein concerned. Theoretical considerations and observation of many cases allow of no other conclusion. Students are still burdened with various tourniquet tests to determine patency of the deep veins. These tests are of interest in that they demonstrate quite strikingly certain features of blood flow and its derangement in cases of venous block and valvular incompetence. It is often possible to locate the level of communications between deep and superficial systems, but in my experience this is usually either obvious from the pressure of a thumb at the appropriate level or still doubtful after repeated application and removal of tourniquets at different levels. While not denying the occasional clinical usefulness of tourniquet tests when simpler methods fail, I suggest that their practical value is small and that their real place is in the applied physiology class.

Dr. Anning mentions having seen disastrous results of treating superficial varices in several patients. There are two explanations. First, this is a progressive disease; both extension of thrombosis and recanalization of blocked deep veins may worsen the venous stasis. Secondly, I suspect that those patients who have been notably worse soon after treatment have had their varices injected as well as, or instead of, ligated. The risk of sclerosants causing further deep thrombosis must be small, since many surgeons of experience have employed them in these cases for years, but I believe the method to be unsound and that it should not be used for patients who have or have had deep thrombosis.

That ligation of superficial varicose veins is by no means the whole answer to gravitational ulcer is obvious, but it is a valuable method of treatment, and it does in fact have a rational basis. The veins are derelict. Their contribution to the circulation is one of sabotage, hampering the work of such veins as are still endeavouring to maintain the circulation.—I am, etc.,

Bristol. H. J. CROOT.

SIR,—Dr. S. T. Anning (August 27, p. 458) has performed a valuable service in dispelling some of the mist which obscures our understanding of ulceration of the legs. His main conclusion will bear restatement: so-called varicose ulcers are not the result of varicose veins. A long experience of the cases seen in a varicose-vein clinic has convinced me of the truth of this after having observed: (1) that the great majority of leg ulcers occur in patients who either have no varicose veins or have varicosities which from their small size or number or by their remote situation cannot be regarded as the cause of the ulcers; (2) that vast numbers of people with varicose veins of long standing and of every degree of severity never develop ulcers.

Recognition of these simple facts suggests one immediate line of progress—to abandon the term "varicose ulcer." This in itself would do much to promote a more rational approach to the whole problem. What name should we use in its place? Dickson Wright's term "gravitational ulcer" goes straight to fundamentals in so far as the elimination of the effect of gravity is the most potent single factor in curing these ulcers. It is, however, insufficiently comprehensive to cover the syndrome, which, besides ulceration, may include oedema, induration, and eczema, and whose most distressing symptom is pain. Bauer's term, "lower leg syndrome," acknowledges the multiplicity of the manifestations of the malady, but it is cumbersome and omits reference to the effect of gravity. "Gravitational syndrome" suggests itself as an improvement.

Concerning aetiology, the emphasis in Dr. Anning's paper is upon a pre-existing thrombosis of the deep veins of the leg and thigh. In questioning my own patients, however, I have been puzzled by my frequent failures to obtain a history of "white leg" or other thrombotic manifestation. For a time, convinced as I was that the fault lay in the deep veins, I thought that a "silent" thrombosis must have been the cause in the majority of these cases of gravitational syndrome. I have sought confirmation of this by phlebography, surgical exploration, and biopsy.

Bauer[1] has pointed out that for this purpose injection of the contrast medium into the small saphenous vein behind the external malleolus is of little value. Not only is the filling of the deep veins very uncertain by this method, but, since the contrast medium follows the normal direction of flow of the venous blood, an identical appearance is given by a patent femoral vein whether or not the valves are competent. These objections are overcome by using Bauer's method of retrograde injection. The patient is tilted feet down at an angle of 45° and the injection is made into the upper end of the femoral vein. The radio-opaque substance flows down the vein by gravity.

If the vein is normal the medium is held up by the first valve an inch or two below the point of injection, and below this the radiograph shows no shadow or only a very faint one. If the vein has deficient valves the medium immediately drops along the whole length of the femoral and popliteal veins into the deep veins of the leg. The cusps of the valves are usually visible, indicating that they are functionally incompetent but neither congenitally absent nor destroyed by disease. If the vein has been previously thrombosed and recanalized a narrow, irregular channel replaces the normal broad, smooth appearance, or a leash of fine satellite vessels derived from the adventitia is substituted for it. No trace of valves is visible.

In the cases of gravitational syndrome which I have investigated by retrograde phlebography I have been struck by the preponderance of femoral veins of wide calibre and smooth outline showing total or partial incompetence of the valves. Surgical exploration of these veins has revealed no periphlebitis. Microscopical examination of pieces excised shows either a normal appearance or varying degrees of fibrosis of the media with degeneration of the intima but no evidence of thrombosis.

It seems, therefore, that the statement made by these patients that they have had no previous thrombosis is true, confirmed as it is by phlebography, surgical exploration, and histological examination. Bauer has called these cases of gravitational syndrome "idiopathic," and the cause of the dilatation and valvular incompetence of the deep veins may be a combination of wear and tear, hereditary weakness, and such metabolic disorders as those at which you hint in your annotation (p. 480).

As regards treatment, we know that practically all gravitational ulcers can be healed by sufficiently prolonged recumbency and many by the continuous support of suitable bandages. The problem suggested by the foregoing observations is whether this slow process of healing can be appreciably hastened by permanent interruption of the femoral or popliteal vein to remove the hydrostatic pressure of the contained column of blood from the vessels of the lower part of the leg. It is certain that the indiscriminate performance of the operation of high saphenous ligature is not the right treatment of gravitational syndrome.

Dr. Anning is to be congratulated on giving an impulse to the critical examination of the question of what may be achieved by surgical attack on the deep veins.—I am, etc.,

Edgware, Middlesex. FRANK FORTY.

REFERENCE

[1] *J. int. Chir.*, 1948, **8**, 937.

Amoebiasis in England

SIR,—I was very interested to read somewhat belatedly the article by Drs. A. R. D. Adams and D. R. Seaton (July 16, p. 136) referring to amoebiasis in England. Had the cases occurred in, say, Rugby or Cambridge they would, I think, have been of more interest, but occurring in Liverpool they are surely not unexpected. Liverpool is a seaport and has a floating population of seamen, including Lascars and Indonesians who come from places where the cyst-carrier rate is high. They also do not share our own ideas of hygiene. Apart from the ship's officer and the doubtful infection by the father who was born in India (though a case has occurred in Australia, where amoebic dysentery is non-existent, of a relapse 20 years after contraction in Gallipoli, and which, incidentally, went on to liver abscess) some surprise seems to be voiced on the occurrence. One of the families contained a docker, and it is not unreasonable to suppose that all had contacts with dockside folk, and, as has been pointed out, they were all from unhygienic surroundings.

I must also take exception to the term "acute" amoebic dysentery. Amoebic dysentery, as seen by the vast majority of Service and colonial doctors, is a chronic or, at worst, a sub-chronic disease, in that if untreated or incompletely treated it takes many years to kill, if at all—the majority of cases clearing up and becoming cyst carriers. Even Manson-Bahr only admits to seeing a "few cases only" of acute amoebic dysentery. It has been left to workers in Java and on the Burma-Siam "railway of death" to see the real acute amoebic dysentery. These cases pass up to 40 to 50 stools per day and die in about 10 to 14 days, if untreated, in great agony—conscious to the last, with vomiting and maniacal symptoms.[1] —I am, etc.,

Tripoli. LENNOX MACFARLANE.

REFERENCE

[1] MacFarlane, L. R. S., *J. R. Army med. Cps*, 1947, **89**, 223, 255.

Memorial to Charles John Bond

SIR,—It has been decided in Leicester to raise a fund for a memorial to the late Charles John Bond, C.M.G., F.R.C.S., and it is thought that there may be friends of his elsewhere who would like to know about this project and be given an opportunity of showing their appreciation.

Bond was born in Leicestershire in 1856, and after his training at University College Hospital, London, he returned to live and work in Leicester until his death in 1939. He was pre-eminently a scientist, and his publications, which are very many and of great interest, show his surgery to have been far ahead of his time. His work was done in the Leicester Royal Infirmary, but also, as was the custom in those days, often in the patient's home in the country under very simple conditions. In an exceedingly busy life he never ceased from original and experimental research. This he did in a wide range of subjects which brought him international recognition. He began with two papers on anatomy as a student, passing in turn to surgery, gynaecology, haematology, and genetics. The breeding experiments in birds and plants were carried out in his own garden. For 40 years he was the close friend of the late Sir Victor Horsley, F.R.S., and Bond showed in his book *Recollections of Student Life and Later Years* how closely their work was integrated.

During the 1914–18 war he was gazetted honorary colonel in the Army Medical Service and became consulting surgeon (with the late Lord Moynihan) to the Northern Command. He was a member of the Medical Research Council of the Privy Council, and he represented the Medical Research Council on the Inter-Allied Commission on Treatment of War Wounds held in Paris from 1916 to 1918. During these years he studied wounds, immunity, the effect of antiseptics on body tissues, and leucocyte activity, finding time to publish his own observations; these are of particular interest to read in relation to the work done in these subjects in the second world war 25 years later. Throughout his work, in all its ramifications, he correlated his wide experience and philosophy with the sociological problems of the times. Were he alive to-day he would undoubtedly have been keenly interested in the State Service which he foresaw as early as 1912. Nothing was too big to daunt him nor too trivial to be ignored. He observed, recorded, and deduced with courage, but there was a characteristic humility and consideration for the opinions of others.

Surely it must be unique for a surgeon to have carried out so much valuable work on so many subjects, based on a sound pathological foundation, unattached to any of the great teaching hospitals. Bond decided to work in the provinces, where, it is true, the material is always abundant and good but where there was no medical school, and for many of the earlier years of his life there was no laboratory accommodation. It seems fitting that such a life should be commemorated for our inspiration.

It is proposed to place a plaque in the Leicester Royal Infirmary and also to create a fund to enable students in biology at the Leicester University College to have greater opportunities for research and travel. Any contribution to this memorial should be sent to the Honorary Treasurer, Dr. L. K. Harrison, 2, Springfield Road, Leicester.—We are, etc.,

JOAN B. WALKER.
N. I. SPRIGGS.
Joint Hon. Secretaries.

Leicester.

Family Planning

SIR,—I receive literature from the Family Planning Association in which the following adequate reasons for family limitation are recognized: (*a*) too many children already (6 to 15); (*b*) "younger married women who are determined not to be driven into the slums, as their parents were driven, by the birth of a child year after year, on an income hopelessly inadequate to support them."

For many years now I have been dealing in my practice with women of all ages and economic groups who are led to seek my advice on contraception. My yardstick is this: Here we have a woman of child-bearing age who prefers not to conceive. She is recognized by the laws of this country as being a fit and proper person to vote at any election, to be conscribed for military purposes, to sit in the Lower House, to become a magistrate, and, in general, to be entitled to sex equality. I do not inquire into the particular personal reason the woman may have in seeking my advice. Subject to whatever interpretation one may feel inclined to put upon the marriage vows, and given always the husband's approval, I inquire no further. From that point on I consider that my position is purely that of technical adviser. Am I wrong?—I am, etc.,

Worthing. O. P. CLARK.

The Osler Family

SIR,—I am glad I wrote (July 9, p. 45) that Edward Osler's well-known hymn is *almost* the sole survivor of many, for in the same issue (*Supplement*, p. 40) in the account of the official religious service at Harrogate a much better-known hymn, "Praise the Lord, ye heavens adore Him," is ascribed to him under the disguise of "Ostler." The two authentic verses of that hymn are anonymous, but derived from the Foundling Hospital's eighteenth-century collection, and to that extent medical. In some books—e.g., the *English Hymnal*, 1906, Oxford, number 535—a third verse, by Edward Osler, is added. In some other books it is entered as a separate hymn: it begins, "Worship, honour, glory, blessing, Lord, we offer to thy name."

The name, which a Greek scholar once fancifully derived from *Oiseleur* (fowler), is, of course, the same as Ostler, though William Osler's family pronounce the *o* long, like "owe-slur." The word has descended in the scale of respectability. In the thirteenth century, when names became hereditary, it meant a hosteler, from *hospitalarius*, appropriately having to do with guests.—I am, etc.,

Montreal. W. W. FRANCIS.

POINTS FROM LETTERS

Percussion Finger

Dr. Z. P. FERNANDEZ (Leeds) writes: Dr. A. Niven Robertson's personal note on "percussion finger" (August 20, p. 440) interested me, apart from his being one of the pioneer municipal tuberculosis clinicians of the period following the 1914–18 war. In 1925, as chief clinical T.O., Leeds (population 500,000, with the highest known notification of 1,869 tuberculosis cases), a prominent "hoof," as my staff then styled it, was found on the dorsum of the terminal phalanx of my middle finger, nearer the proximal end. The swelling was not painful but very noticeable and distinctly palpable. Though I left municipal service two years later, the nodule is still palpable though not so noticeable.

Reform in Medical Education

Dr. H. M. FLANAGAN (Lincoln) writes: There is a tendency nowadays among some to lean more and more on the usually overworked laboratory at the expense of clinical methods. The trend towards the ultra-mechanistic approach to the human organism, in a rashly enthusiastic effort to force the invaluable scientific method in medicine, is one which will ultimately lead to more confusion and final sterility. In medical education one commences with an interest in sick people, but is invited to begin with molecules and atoms. Perhaps to start with medicine and work back through anatomy and physiology to chemistry and physics is impractical, but it is the natural process of the inquiring mind, confronted with a complaining patient, to work back to understand his disorder in terms of fundamentals like biochemistry. It would tend to follow the history of medicine and so keep the student's interest at a similar high level to that of medical pioneers down the centuries.

Obituary

F. HERNAMAN-JOHNSON, M.D., F.F.R.

With the death of Dr. Francis Hernaman-Johnson at the age of 70, on September 3, British radiology has lost another of the few remaining pioneers in this branch of medicine. Dr. Hernaman-Johnson was physician to the Charterhouse Rheumatism Clinic for many years and chairman of the council of the British Rheumatic Association.

Francis Hernaman-Johnson was born at Crosby, Lancashire, and was educated at the Merchant Taylors' School there. He went on to study medicine at Aberdeen University, where he graduated M.B., Ch.B. with honours in 1904, proceeding M.D. in 1910. He obtained the Cambridge D.M.R.E. in 1931, and in 1939 was a foundation fellow of the Faculty of Radiologists. As a student he won many prizes and honours, including a Liddell bursarship, the first medal for advanced physiology in 1902, and the Duthie scholarship a year later.

Part of his clinical training was undertaken at St. Bartholomew's Hospital, and after graduating he joined the Royal Navy, serving for three years, some part of which he spent at the Royal Naval Hospital, Plymouth. On leaving the Navy, Hernaman-Johnson went into practice at Bishop Auckland, Durham. At that time he was interested in electrotherapy, and it was almost inevitable that he should be attracted to the growing field of radiological work, a part-time activity expected of many electrotherapists in those early days. Soon he was appointed consultant radiologist to the Darlington Education Committee. During the 1914–18 war he was attached to the Cambridge Hospital, Aldershot, and was consulting radiologist and electrotherapist to the Aldershot Command, being mentioned in dispatches for his services. After the war he settled in London.

Dr. Hernaman-Johnson was consulting radiologist to the French Hospital, and he was on the honorary staff of the Croydon General Hospital, the Margaret Street Hospital for Diseases of the Chest, and the Carshalton Memorial Hospital. He had been a member of the Roentgen Society since 1911 and was a member of the council in 1926. He was president of the Section of Radiology of the Royal Society of Medicine in 1934–5, and was the first Warden of the recently formed Faculty of Radiologists. He was also the first Skinner Lecturer of the Faculty.

Right from the early days Dr. Hernaman-Johnson took a great interest in the use of *x* rays in therapy and especially in the treatment of rheumatism. This interest continued throughout his life, and he contributed numerous papers to this and other journals on such subjects as the value of *x* rays in chronic arthritis, constitutional effects of *x* rays, the relative values of *x* rays and radium, and on radiotherapy from many other aspects.

Dr. Hernaman-Johnson was an expert and thorough worker, always anxious for the progress and advancement of his specialty. He never spared himself, and he inspired confidence in his patients and his colleagues. In recent years he had devoted much of his time and energy to the British Rheumatic Association. He was active in promoting schemes for occupational therapy and rehabilitation and for providing homes where patients could rest in between courses of treatment. He brought the same keen interest to his work for the Scientific Advisory Committee of the Empire Rheumatism Council.

One other facet of Hernaman-Johnson's many activities should also be recorded. Using the pseudonym "Francis Wimbrook," he wrote a number of articles for the lay press, and a "psychological thriller" called *Accident* which was staged at the Richmond Theatre. A novel, *Behold the Axe!* was published only last year.—R.J.R.

H. LESLIE-ROBERTS, M.D.

Dr. Hugh Leslie-Roberts, who died on September 8 at his home in Heswall, Cheshire, at the age of 89, was formerly consulting physician to the skin department of the Liverpool Royal Infirmary. He retired from practice in 1938, and his wife, who was the daughter of Mr. Samuel Parker, died only a few weeks ago.

Hugh Leslie-Roberts, the son of Alderman J. F. Roberts, of Manchester, was born in 1860 and began his education at Owens College, Manchester. Subsequently he studied in Edinburgh, where he graduated M.B., C.M. in 1887, proceeding M.D. in 1893. He also spent some time on post-graduate studies in Hamburg and Berlin, and in Paris and Vienna. It was in 1890 that he settled in Liverpool, and three years later he was appointed to the staff of the Liverpool Royal Infirmary. For many years he was lecturer on diseases of the skin at Liverpool University, and apart from his contributions to the medical press he published a treatise on mould fungi parasitic on man. As early as 1894 he was secretary of the Section of Dermatology at the annual meeting of the B.M.A. He was vice-president of the Section in 1904 and 1912 and president in 1922.

Dr. ARTHUR CECIL HINCKS died in the Wells Cottage Hospital on August 26 after a long period of ill-health. He was born at Hay, Hereford, in 1882, and was educated at Christ Church College, Brecon, and Birmingham University, where he played in the rugby fifteen and was captain of the hockey eleven. He graduated M.B., Ch.B. in 1906, and after holding resident appointments at the General Hospital, Birmingham, he came to Wells in 1909 as a partner of Dr. Allan and Dr. Lauder Smith. At the outbreak of the 1914–18 war Dr. Hincks joined the 4th Somersets, but before they left for India he was transferred to the 26th Field Ambulance and went to France with the Expeditionary Force. For conspicuous gallantry and devotion to duty he was awarded the Military Cross in 1915. In the recent war he served as a major in the local Home Guard and was also an A.R.P. lecturer and instructor. He took an active part in the work of the British Legion and had been president of the local branch. For many years Dr. Hincks had been medical officer of health for the city of Wells and senior physician at the cottage hospital. He was a keen churchman and had held office as sidesman and churchwarden. Despite all these and many other interests he found time to serve his colleagues on the local medical and panel committee and on the Somerset Insurance Committee. He was chairman of the East Somerset Division of the British Medical Association in 1932–3; a representative on the Branch Council from 1934–48; representative of the Division in the representative body in 1941 and from 1943–48, when he resigned on account of ill-health. He was also a member of the Local Medical War Committee from its inception. With his passing the people of Wells have lost a family doctor who will ever be remembered with respect and affection by all those with whom he came in contact. To Mrs. Hincks and the members of his family the deepest sympathy is extended by all his colleagues. —G.E.M.

Mr. HARRY VERNON WELLS died on September 2 at Sanderstead, Surrey, at the age of 49. A student at Charing Cross Hospital, he graduated M.B., B.S. in 1926 and went on to take the F.R.C.S. three years later. He was resident casualty officer and later surgical registrar at his teaching hospital.

J.B.S. writes: I must express the heartfelt sorrow his partners and patients feel. It is safe to say there was no man more loved by those who knew him. Wells had been in Sanderstead for seventeen years. He came here with an established reputation, both from Charing Cross, where his chiefs could not speak highly enough of him, and from Birmingham, where he worked for some years. When he joined me in practice here I could see at once what a marvellous technique he had, especially in abdominal surgery. His cases, of course, included every branch of general surgery. There were a number which I referred to him quite hopelessly, but his technique and optimism triumphed over and over again. I have never met a better man: he was uniformly courteous, always sincere and kind. That is not to say he was not firm, even obstinate, about some things, but he always knew his own mind. In the long years of our friendship he never once failed my partner and myself in any difficulty, and we shall miss him greatly.

He volunteered for service in the Army or Air Force at the beginning of the war and again later on, but he was refused by the medical board. He was very troubled about this, and wrote to the president of one of the boards complaining that somebody must have misunderstood his condition, as he felt in perfect health and was quite able to undertake any effort. A very kind letter from the president of the board comforted him, but he was assured that he would not be accepted. However, surgical work in connexion with Purley Hospital was quite sufficient to give him far more to do than he ought to have done. There were very few surgeons left in this district, and there was hardly a night when Wells was allowed to sleep in peace during the war years. He was sent for in every important emergency and for most major operations. I think it sad that no public acknowledgment has been made of his services so freely and unselfishly given, though his friends let him see how much they valued him and his work. I want to express everybody's sympathy with his wife, Dr. Mary Wells, in her loneliness and bereavement.

Medico-Legal

BREACH OF TERMS OF SERVICE

N.H.S. Patient Charged a Fee

A report from the Medical Service Committee which was adopted by the Executive Council for the County of Surrey on March 9 gave the findings of the committee in three cases of complaints against doctors. One was dimissed as frivolous, on another no action was recommended, and in the third case the doctor was held to be at fault.

In this instance the complainant's written statement alleged failure on the part of the doctor to comply with the terms of service in that he (*a*) made a perfunctory examination; (*b*) uttered remarks to which the complainant took exception; (*c*) in issuing a medical certificate used an incorrect form for the purpose; (*d*) demanded and accepted a fee of five shillings; and (*e*) ordered drugs required for treatment on a form other than that supplied by the council. In the view of the committee the following facts were established. The complainant was accepted by the doctor for inclusion in his list, and on several occasions before this complaint was made the complainant had received treatment as a registered patient. On September 23, 1948, the doctor carried out an abdominal examination of the patient and took his temperature. During the course of this visit the doctor made observations inconsistent with the dignity of his profession. He then ordered the drugs needed on a form other than that provided by the council, and he issued a private certificate. The doctor then demanded and accepted a fee of five shillings in respect of his treatment of the patient.

On October 18 the patient wrote a letter asking for a receipt for the five shillings which had been paid. On October 19 the doctor issued a receipt on a form provided by the council in respect of treatment given under Paragraph 5 (2) of the First Schedule to the National Health Service (General Medical and Pharmaceutical Services) Regulations, 1948.

The committee agreed that certain inferences might properly be drawn from these facts. (1) The doctor was aware that he

had accepted the complainant for inclusion in his list. (2) The doctor carried out a satisfactory examination and ordered such drugs as he considered necessary. (3) The doctor failed to comply with the terms of service, however, in that he ordered drugs for the treatment of the complainant on a form other than that provided by the council, and in that he demanded and accepted a fee in respect of the treatment given.

The committee therefore recommended that the council should recover from the doctor, by a deduction from his remuneration, expenses incurred by the complainant owing to the failure of the doctor to comply with the terms of service, and that the council should make representations to the Minister of Health that, owing to the failure of the doctor to comply with the terms of service, the sum of ten pounds should be withheld from his remuneration.

Universities and Colleges

UNIVERSITY OF BIRMINGHAM

Humphrey Francis Humphreys, M.B., Ch.B., M.D.S., F.D.S. R.C.S., Professor of Dental Surgery in the University, has been appointed Vice-Principal of the University from September 30 in succession to Professor M. L. E. Oliphant, F.R.S., Poynting Professor of Physics.

SOCIETY OF APOTHECARIES OF LONDON

Professor E. C. Dodds, F.R.S., Master, presided at recent meetings of the Court of Assistants, at which Mr. Duncan C. L. Fitzwilliams was elected Master from August 24 and Dr. Frank Howitt and Dr. G. Roche Lynch were elected Wardens.

The report of the sudden death through an accident of Dr. Christopher Thackray Parsons, Past Master, was received with regret.

John Francis Carter-Braine took his seat upon the Court of Assistants.

The following appointments were made: Mr. L. Vernon Cargill to the Chelsea Physic Garden Committee of Management for a further four years from August 20; Professor Dodds to the Ministry of Health Joint Committee in connexion with Part IV of the National Health Service Act; Sir Cecil Wakeley to the British Postgraduate Medical Federation for a further year from October 1.

Mrs. Cecil Wall presented a large collection of manuscripts by the late Dr. Cecil Wall, Archivist, on the history of the society and its hall.

The following were granted the Diploma in Industrial Health upon examination: J. A. Herd, C. N. D. Cruickshank, C. Crowley, G. G. Mathew, W. G. White.

The Diploma, L.M.S.S.A., was granted upon examination to the following: H. T. H. Beach, J. L. Jarvis, D. Redpath, G. E. Hanks, F. W. Retief, M. P. Cardew, K. C. Horrocks, E. M. Tiger, H. V. White, M. P. M. Coupland, R. J. Aspinall, C. J. G. Menzies, C. R. May, M. C. H. Jackson, H. E. G. Dyer, F. Walton, F. E. Bramwell, E. R. Goodall, D. J. Joubert, G. B. Stephenson, W. G. Burvill Holmes, G. T. Cecil, G. A. R. Giri, P. B. Poole, A. K. Kantarjian, L. Kader, J. D. Morris, C. T. Jones, E. W. Melia, M. C. Gilbert, A. S. Murad.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

The William Meredith Fletcher Shaw Memorial Lecture will be delivered by Professor R. W. Johnstone, C.B.E., M.D., F.R.C.S.Ed., F.R.C.O.G., at the College, 58, Queen Anne Street, London, W., on Wednesday, October 12, at 2.30 p.m. His subject is: "Scotland's Contribution to the Progress of Midwifery in the Eighteenth and Early Nineteenth Centuries." An invitation is extended to doctors interested in the subject, but admission is by ticket only, obtainable from the secretary.

The Services

The announcement of the award of the Efficiency Medal (Territorial) to Captain (now Temporary Lieutenant-Colonel) A. B. Dick, R.A.M.C., in the *London Gazette* of May 2, 1947, and printed in the *Journal* of May 31, 1947 (p. 789), is deleted in a list of errata published in a *Supplement* to the *London Gazette* dated August 12, 1949.

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended August 27. [No. 34

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland, (d) Eire. (e) Northern Ireland.

Figures of Births and Deaths, and of Deaths recorded under each infectious disease, are for: (a) The 126 great towns in England and Wales (including London). (b) London (administrative county). (c) The 16 principal towns in Scotland. (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland.

A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

Disease	1949 (a)	(b)	(c)	(d)	(e)	1948 (Corresponding Week) (a)	(b)	(c)	(d)	(e)
Cerebrospinal fever	18	2	16	2	—	29	4	14	1	—
Deaths		—	—				1	—		
Diphtheria	52	6	25	—	3	123	11	34	10	5
Deaths	1	—	—	—	—	1	1	1	—	—
Dysentery	90	10	68	1	—	70	9	55	5	—
Deaths				—	—				—	—
Encephalitis lethargica, acute	2	—	—	—	—	2	1	1	—	—
Deaths		—					—			
Erysipelas			17	8	5			28	15	1
Deaths		—					—			
Infective enteritis or diarrhoea under 2 years				74					40	
Deaths	28	2	3	9	—	24	—	10	1	2
Measles*	1,778	120	75	68	41	3,774	149	25	11	15
Deaths†			—	—	—			—	1	—
Ophthalmia neonatorum	38	2	8	—	—	55	6	10	—	—
Deaths										
Paratyphoid fever	25	3	—	7 (B)	—	17	3	1 (B)	—	—
Deaths	—	—	—	—	—	3	2	—	—	—
Pneumonia, influenzal	222	9	—	—	12	240	16	—	2	3
Deaths (from influenza)‡	3	—	1	1	—	4	1	—	—	—
Pneumonia, primary			74	19				95	16	
Deaths	122	20		3	7	99	9		1	3
Polio-encephalitis, acute	22	5				7	—			
Deaths										
Poliomyelitis, acute	258	29	9	—	1	70	6	3	2	—
Deaths§	20	4				3	—			
Puerperal fever		—	5				2	5		—
Deaths										
Puerperal pyrexia‖	91	7	9	—	—	100	8	10	—	—
Deaths		—					—			
Relapsing fever	—	—			—	—	—			—
Deaths										
Scarlet fever	718	53	131	40	59	812	42	191	52	17
Deaths†			—	—	—			—	—	—
Smallpox	—	—	—	—	—	—	—	—	—	—
Deaths				—	—				—	—
Typhoid fever	10	1	1	4	—	12	1	3	—	—
Deaths	—	—	—	—	—	—	—	—	—	—
Typhus fever	—	—	—	—	—	—	—	—	—	—
Deaths				—	—				—	—
Whooping-cough*	1,671	79	66	69	72	3,162	248	60	48	8
Deaths	3	1	—	—	—	7	2	—	—	—
Deaths (0–1 year)	260	35	32	30	11	247	32	37	10	7
Infant mortality rate (per 1,000 live births)										
Deaths (excluding stillbirths)	4,054	648	517	144	88	3,955	619	533	134	91
Annual death rate (per 1,000 persons living)			10·4	8·9				10·8	8·4	
Live births	7,297	1143	866	410	227	7,298	1234	903	398	236
Annual rate per 1,000 persons living			17·4	25·4				18·2	24·9	
Stillbirths	189	14	33			222	18	30		
Rate per 1,000 total births (including stillborn)			37					32		

* Measles and whooping-cough are not notifiable in Scotland, and the returns are therefore an approximation only.

† Deaths from measles and scarlet fever for England and Wales, London (administrative county), will no longer be published.

‡ Includes primary form for England and Wales, London (administrative county), and Northern Ireland.

§ The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, London (administrative county), are combined.

‖ Includes puerperal fever for England and Wales and Eire.

EPIDEMIOLOGICAL NOTES

Food-poisoning at Llanelly

The recent outbreak of food-poisoning at Llanelly due to *Salmonella typhi-murium B* started explosively on August 15, when 62 cases were notified, and rapidly tailed off within a week, although some cases from secondary "cropping" have been notified since. Altogether 214 cases have been notified, and of these 142 were seen in the first three days.

The source of the infection was a large tin of artificial cream at a pastry shop, where five carriers were discovered; the cream was being used "cold" in the finishing of the pastries. In the course of the investigation five carriers were also discovered in an ice-cream shop, but no contamination of the ice-cream appears to have occurred. The source of infection of the carriers themselves is problematical, sporadic cases of the disease having occurred in the area since the large outbreak at Ammanford three years ago, which was traced to a butcher's assistant infecting cold made-up meats. This butcher's assistant, from the evidence available, appeared to have been infected originally by eating unwashed imported fruit.

The infection was generally mild. The presenting symptoms were diarrhoea and vomiting, which usually came on within 24 hours and only exceptionally lasted longer than three days. Of the 12 cases admitted to hospital only three were seriously ill: an old lady of 80, a young man of 20, and a baby who had a congenital defect. Chloromycetin appeared to have a beneficial effect on these three cases. A man of 63 who was also affected died in hospital from coronary thrombosis a week after admission. Post-mortem examination revealed no trace of the *Salmonella* infection, and confirmed the recent coronary thrombosis with widespread arteriosclerosis and myocardial degenerative changes.

Poliomyelitis

Notifications in England and Wales for the week ended September 3 were poliomyelitis 289 (258), polio-encephalitis 19 (22). Figures for the previous week are shown in parentheses.

The fluctuation during the past three weeks is not considered to have any special significance. The rise to 308 notifications since the last report should not be taken as indicating the likelihood of any further rises of considerable magnitude.

The multiple cases in counties were as follows: London 43 (34), Berkshire 5 (3), Chester 3 (0), Cornwall 5 (5), Cumberland 1 (1), Derby 2 (2), Devon 7 (4), Dorset 2 (2), Durham 8 (3), Essex 21 (13), Gloucester 13 (14), Hertford 3 (6), Huntingdon 2 (0), Kent 10 (9), Lancaster 28 (33), Leicester 11 (1), Lincolnshire, Kesteven 2 (0), Lincolnshire, Lindsey 5 (3), Middlesex 18 (17), Northampton 3 (4), Northumberland 10 (6), Nottingham 6 (7), Somerset 9 (6), Southampton 10 (16), Stafford 3 (4), Suffolk East 2 (1), Surrey 7 (5), Sussex East 2 (5), Sussex West 3 (2), Warwick 8 (7), Wiltshire 4 (3), Worcester 4 (0), Yorkshire West Riding 37 (33), Glamorgan 5 (1).

Discussion of Table

In *England and Wales* there was a decrease in the notifications of measles 342 and acute poliomyelitis 15. Increases were recorded in the incidence of dysentery 55, scarlet fever 40, and whooping-cough 34.

A decreased incidence of measles was recorded in practically all areas; the largest falls were Kent 62, Middlesex 45, Lancashire 44, and Yorkshire West Riding 44. The only notable exceptions to the general trend for measles were increases in the notifications in Durham 52 and in the rural district of Cambridgeshire 37. There were no large changes in the local returns of scarlet fever.

The largest fluctuation in the incidence of whooping-cough was a rise of 36 in Durham. Notifications of diphtheria were 7 below the record low level of last week.

The rise in the incidence of dysentery was due to two outbreaks, one affecting 29 persons in Staffordshire, Wolverhampton C.B., and the other with 25 notifications in Monmouthshire, Rhymney U.D. There were 9 cases of paratyphoid fever in Lancashire. The largest number of notifications of food-poisoning was in Carmarthenshire, Llanelly M.B. 22 (see above).

In *Scotland* there were falls in the notifications of acute primary pneumonia 53 and dysentery 15 and rises in the incidence of whooping-cough 25 and measles 18. In Glasgow 46 of the 68 cases of dysentery were notified. There was also an increase of 9 in the notifications of cerebrospinal fever in Glasgow.

In *Eire* decreases were recorded in the notifications of whooping-cough 49, measles 28, and scarlet fever 21, while the incidence of diarrhoea and enteritis rose by 12. Of the 74 cases of diarrhoea and enteritis 62 were notified in Dublin C.B.

In *Northern Ireland* the notifications of scarlet fever increased by 16, while a fall of 10 was recorded in the incidence of whooping-cough. The rise in the notifications of scarlet fever was due to the experience of Belfast C.B.

Week Ending September 3

Notifications of infectious diseases in England and Wales during the week included: scarlet fever 701, whooping-cough 1,615, diphtheria 53, measles 1,168, acute pneumonia 216, cerebrospinal fever 25, acute poliomyelitis 289, acute polio-encephalitis 19, dysentery 98, paratyphoid fever 30, typhoid fever 9, food-poisoning 277.

Medical News

Oliver Memorial Fund

The committee of this fund has made the second award for service in connexion with blood transfusion to Dr. H. F. Brewer, clinical pathologist to St. Bartholomew's Hospital. Dr. Brewer has been medical officer to the British Red Cross London Blood Transfusion Service for 16 years, and has been intimately connected with the development of this pioneer service. His attention to the welfare of the donor has engendered a spirit of confidence among the members, and data obtained from the periodic examination of donors after multiple bleedings established the safe minimum intervals between donations for males and females. In the years immediately before the war the Red Cross Service made the first provision for the distribution of reliable and cheap anti-A and anti-B grouping sera, and Dr. Brewer played a significant part in ensuring this. His influence was continued throughout the war as director of one of the London blood supply depots.

Association des Médecins de Langue Française

The *Association des Médecins de Langue Française* was founded in 1911 to facilitate contacts between French-speaking doctors in different countries. The association arranges conferences in French-speaking countries to bring members together for discussion of various medical questions. Between the two wars the association had several hundred members in France and in other countries, and a conference was held every other year. Since the end of the war one meeting took place in Paris in 1947, and a second is planned for this October in Geneva. New members will be cordially welcomed, and the secretary, Professor Cade, would greatly appreciate information about changes of address from former members, particularly from those living outside France. The registered office of the association is at the Faculty of Medicine of Lyons, and all details about membership can be obtained from Professor A. Cade, 10, rue de la Charité, Lyon, Rhône.

Wills

Dr. Charles William Menelaus Hope, formerly consulting surgeon for diseases of the ear, nose, and throat to King's College Hospital, left £39,375. After making a number of bequests he left the residue of his estate as to one-third to King's College Hospital, and two-thirds to King's College Hospital Medical School. Dr. Henry Wilkes Gibson, of Emsworth, Hants, left £32,538; Dr. William Gordon Alexander, of Broadway, Worcs, left £6,008; Dr. Harold Godfrey Young, of Hatfield, Herts, left £7,492; and Dr. John Donald Matheson MacKellar, of Dewsbury, Yorks, left £10,165.

COMING EVENTS

British Rheumatic Association Exhibition and Conference

The British Rheumatic Association has arranged a two-day conference to be held at Chelsea Town Hall, London, S.W., on Wednesday and Thursday, September 28 and 29. The opening address, on "Modern Views on the Treatment of Rheumatoid Arthritis," will be delivered on September 28, at 2.30 p.m., by Dr. W. S. C. Copeman, and at 5 p.m. Dr. W. S. Tegner will discuss "The Care of the Rural Patient." On September 29, at 2.30 p.m., addresses will be given by Miss Nora Hill, Principal of the Disablement Branch of the Ministry of Labour, and Air Commodore G. O. Venn, Executive Director of "Remploy," Ltd., and at 5 p.m. there will be a symposium on "The Homebound Employed," in which the special problems of rheumatic patients will be presented from the points of view of the doctor, the industrialist, and the patient by Dr. Francis Bach, Mr. Sydney Arthur, and Miss B. M. Stow, Chairman of the Association of Occupational Therapists, respectively. Tickets for the conference (price 10s. each) will be allocated in order of application. The association has also arranged an exhibition to be held on September 27 (2 p.m. to 10 p.m.), September 28 and 29 (10 a.m. to 10 p.m.), and September 30 (10 a.m. to 6 p.m.), which will be open to the public (entrance fee 1s.). Full particulars may be obtained from the association at 5, Tite Street, Chelsea, London, S.W.3.

Medical Students' Conference

The Glasgow Branch of the British Medical Students' Association has arranged a conference for medical students to be held from September 26 to 30, during which lectures will be delivered as follows: In the Pathology Lecture Theatre, Western Infirmary, Glasgow, Tuesday, September 27, 11.15 a.m., Professor C. F. W. Illingworth, "Peptic Ulcers"; Wednesday, September 28, 11.15 a.m., Professor D. F. Cappell, "The Rhesus Factor"; Thursday, September 29, 11.15 a.m., Dr. T. Anderson, "Antibiotics in the Treatment of Infection"; Friday, September 30, 11.15 a.m., Professor S. G. Graham, "Acidosis and Alkalosis," and 2 p.m., Dr. W. A. Taylor, "Hypertension." On September 30, from 9.15 a.m., there will be a demonstration on hypertension in the pathological department of the Western Infirmary. The following lectures will be delivered in the Zoology Lecture Theatre of the University of Glasgow: Monday, September 26, 4.15 p.m., Professor P. I. Dee, F.R.S., "Nuclear Physics in Medicine"; Tuesday, September 27, 4.15 p.m., Dr. P. R. Peacock, "The Effects of Radiations on Experimental Tumour"; Friday, September 30, 4.15 p.m., Professor L. S. P. Davidson, "Partition Chromatography." Members of the medical profession are invited to attend the lectures.

C.M.F. Surgeons' Club Dinner

The annual dinner of the C.M.F. Surgeons' Club will be held at Claridge's Hotel, Brook Street, London, W., on Thursday, September 29. Applications for tickets, with cheques for 25s., should be sent to Mr. Guy Blackburn, M.Chir., Keat's House, Guy's Hospital, London, S.E.1. Evening dress will be worn. Guest tickets are not available.

Contraceptive Technique

A lecture and demonstration of contraceptive technique will be given by Dr. Marie C. Stopes and Dr. Beddow Bayly at the Mothers' Clinic, 108, Whitfield Street, London, W., on Thursday, October 6, at 2.30 p.m. Medical practitioners should apply for tickets well in advance.

Prevention of Accidents

The Royal Society for the Prevention of Accidents will hold a National Safety Congress on October 4–7 at the Central Hall, Westminster. Among the speakers will be Dr. C. A. Boucher, of the Ministry of Health, and Dr. J. A. Gorsky. Particulars may be obtained from the society at Terminal House, 52, Grosvenor Gardens, London, S.W.1.

Welsh National School of Medicine

The opening address of the 1949–50 session of the Welsh National School of Medicine will be delivered on Thursday, October 6, by Dr. William N. Pickles, Medical Officer of Health for Aysgarth.

SOCIETIES AND LECTURES

Tuesday

EDINBURGH POSTGRADUATE BOARD FOR MEDICINE.—At Anatomy Lecture Theatre, Edinburgh University, September 20, 4.30 p.m., "*Bone and Joint Pathology*," by Professor S. L. Baker.

Wednesday

NORTH-EAST LONDON CLINICAL SOCIETY.—At Clinical Theatre, Prince of Wales's General Hospital, Tottenham, N., September 21, 8.15 p.m., medical films and discussion on public health matters.

Thursday

EDINBURGH POSTGRADUATE BOARD FOR MEDICINE.—At Anatomy Lecture Theatre, Edinburgh University, September 22, 4.30 p.m., "*The Bacteriological Principles Governing Chemotherapy*," by Professor C. H. Browning, F.R.S.

Friday

BIOCHEMICAL SOCIETY.—At Department of Biochemistry, School of Medicine, Leeds, September 23, 11 a.m., 279th meeting.

MIDDLESEX COUNTY MEDICAL SOCIETY.—At Edgware General Hospital, Edgware, Middlesex, September 23, 4 p.m., annual general meeting. "*Focal Hypersensitivity as a Pathological Syndrome*," by Dr. J. L. Hamilton-Paterson.

ROYAL SANITARY INSTITUTE.—At National Museum of Wales (Reardon Smith Lecture Theatre), Cardiff, September 23, 10 a.m., "*The National Health Service Act (Sections 24 and 28): Advice, Care, and Aftercare*," discussion to be opened by Mrs. Clarice O'Shea: "*Food Control*," by Mr. W. M. Shortt, M.Sc., F.R.I.C.

APPOINTMENTS

Drs. F. A. Ibiam, O.B.E., and K. A. Abayomi have been appointed Members of the Executive Council of Nigeria.

HUGHES, A. C. C., M.B., M.R.C.P., Chest Physician, Chester Area, Liverpool Regional Hospital Board.

LANDON, JOHN, M.R.C.S., L.R.C.P., D.P.H., Medical Officer of Health for the Boroughs of Bexley and Erith and Urban District of Crayford and School Medical Officer, Borough of Bexley.

REES, F. T., *M.C.*, M.R.C.S., L.R.C.P., Director-General of Medical Services, Ministry of Pensions, in succession to Sir Francis Prideaux, C.B.E., M.R.C.S., L.R.C.P., who retires on September 30.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

McQuaid.—On September 9, 1949, to Ena (née Green), wife of Dr. T. M. McQuaid, 96, Psalter Lane, Sheffield, a son.

MARRIAGES

Black—Gordon.—On August 20, 1949, at St. Paul's Church, Enfield, Alexander L. Black, M.B., F.R.C.S.Ed., to Jeanie F. Gordon, M.B., D.C.H.

Moore—Hewitson.—On September 1, 1949, at St. Albans Abbey, W. E. Dodwell Moore, M.B., B.Ch., to Nora Hewitson, M.B., B.S.

Smith—Blatherwick.—On September 10, 1949, at Mere, Wiltshire, D. W. G. Smith, M.B., M.R.C.P., D.P.H., to Marjorie Blatherwick.

DEATHS

Densham.—On September 8, 1949, at Parkstone, Dorset, Ashley Densham, M.R.C.S., L.R.C.P., aged 79.

Finn.—On September 11, 1949, at Gatcombe House, Ashwick, near Bath, Patrick Taaffe Finn, L.R.C.P.&S.Ed., L.R.F.P.S.

Forgan.—On September 6, 1949, at Highgate, Robert Berry Forgan, L.R.C.P.&S.Ed., L.R.F.P.S., aged 62.

Gerhard.—On August 29, 1949, at Overbrook, Philadelphia, U.S.A., Arthur Howell Gerhard, M.D., aged 73.

Hay.—On September 8, 1949, Edmund Hay, M.B., C.M.Ed., of 384, Prince Regent's Lane, London, E.

Kearney.—On September 5, 1949, James Kearney, L.R.C.P.&S.I. and L.M.

McCall.—On September 9, 1949, at Rudgwick, Sussex, Annie McCall, M.D.

Martin.—On September 5, 1949, at St. Mary's Hospital, Paddington, London, W., William Whittle Martin, M.B., Ch.B., D.P.H., of the Manor House, Southwick, Sussex.

Moll.—On September 8, 1949, Henry Henderson Moll, M.D., F.R.C.P., aged 53.

O'Connor.—On September 5, 1949, at Old Manor House, Epsom, James Alphonsus O'Connor, M.B., Ch.B., late Indian Army, aged 55.

Roberts.—On September 8, 1949, at Hessle Moor, Heswall, Cheshire, Hugh Leslie Roberts, M.D., aged 89.

Robertson.—On September 6, 1949, at 178, Burnage Lane, Manchester, William Robertson, L.R.C.P.&S.Ed., L.R.F.P.S., aged 78.

Seah.—On August 29, 1949, at Findon, Sussex, Eng Khway Seah, F.R.C.S., aged 50.

Strain.—On September 10, 1949, William Loudon Strain, M.B., C.M., of 4, Hove Court, Raymond Road, Wimbledon Hill, London, S.W.

Walker.—On September 3, 1949, at Aberdeen, James Robert Hall Walker, M.D.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Myasthenia Gravis

Q.—*In view of the antagonism between the action of the thyroid gland and of the thymus, would methyl thiouracil be worthy of trial in myasthenia gravis?*

A.—Thymectomy is of value in myasthenia gravis. An important paper on this subject appears in the opening pages of this issue of the *Journal*. Thyroidectomy is not known to be of any value in myasthenia gravis uncomplicated by thyrotoxicosis, and it is doubtful if it is of value in true myasthenia gravis, which may be present at the same time as thyrotoxicosis but not a sequel to it. On the other hand, thyroidectomy is definitely of value in that form of myasthenia which is a complication of thyrotoxicosis. It is difficult, however, to conjecture that methyl thiouracil would be of any value in idiopathic myasthenia gravis. If it did prove of value it might not be regarded as suitable therapy, because of the need for its persistent application for the duration of the disease. In assessing any form of treatment it must be remembered that myasthenia gravis undergoes spontaneous remissions which may last for many months.

Threadworms in Infants

Q.—*What is the best treatment for threadworm infestation in children under the age of 2? Tablets or capsules are unsuitable for infants because of the inadequate swallowing reflex, and frequent enemata are contraindicated on psychological grounds. Is there anything that can be given in liquid form and still be effective in the large bowel?*

A.—The best treatment for threadworms in an infant under 2 years is gentian violet. The usual plan of dosage is to give 1/6 gr. (11 mg.) daily for each year of age, in divided doses, two or three times a day before meals. The course is usually one of five days with five days' break and then a second five days of the drug. Meanwhile gloves and pyjamas should be worn to prevent night scratching (if napkins have been left off) and a little ammoniated mercury ointment smeared round the anus at night. Unfortunately to give gentian violet there is no satisfactory alternative to capsules, and the administration of these to a young infant is a skilled job. Probably the best solution would be the temporary admission of the child to hospital for each of the five-day periods. If psychological trauma is feared from this, a nurse might visit at home, but the situation demands a nurse trained in work with children, and she is more likely to be successful in hospital. It is worth while remembering that threadworm infestation is often familial, and if a young baby has threadworms then the same may apply to older children or even to the parents, in whom there may be no symptoms. While the infant is in hospital the rest of the family might be investigated and treated if necessary.

Antiseptics for Minor Dressings

Q.—*For constant use in minor dressings acriflavine has the disadvantage that it stains the hands, dressings, towels, etc. Is there any comparably bland antiseptic that does not produce staining (mercury perchloride, for example), and that can be substituted for routine use in the surgery?*

A.—Yes: 5-aminoacridine hydrochloride ("monacrin")—a substance of the same chemical nature as acriflavine, and having a similar action on bacteria and a rather lower tissue toxicity, but non-staining. If the inquirer is referring to prophylactic application to accident wounds there is much to be said for abandoning the use of solutions altogether and thus largely overcoming the difficulty of staining. The alternative method is insufflation of a powder for which the formula in common use is 1 part of proflavine (2:8-diaminoacridine sulphate) in 99 parts of sulphathiazole. Proflavine stains, but for various reasons—notably its constancy of composition, lower tissue toxicity, and lower solubility—is otherwise superior to acriflavine. The advantage of using a relatively much less soluble antiseptic in powder form is that a more persistent effect is obtained than with a solution.

Mercury perchloride is not "bland," it is exceedingly toxic, and should never be applied to any part of the body except, possibly, the intact skin.

Dose of Chloral for a Baby

Q.—*How far can chloral be safely pushed in the symptomatic treatment of restlessness in a newborn child delivered with forceps? Would you consider a four-hourly dose of 1 gr. (65 mg.) harmless if given over a period of two or three days, or could such a dose cause liver damage and/or respiratory embarrassment due to lack of movement brought about by the narcosis? Is it justifiable to give chloral as a routine to "stressed babies"?*

A.—It appears quite safe to give chloral hydrate 1 gr. four-hourly to a newborn child, and this is a recognized form of treatment for infants suspected of cerebral irritation. Usually the dose is gradually reduced as the irritability improves. It is inadvisable to give chloral routinely to "stressed babies." There is usually a cause for the irritability, and this should be sought and corrected. However, there is the irritable infant of a "highly strung" mother that usually responds well to 1 gr. of chloral hydrate before each feed, and this can be continued for several months. Children tolerate chloral very well and rarely show toxic symptoms. It is unlikely to cause respiratory embarrassment in the newborn, but if cyanosis is present oxygen could be given.

Dermatitis Due to Cold Permanent Waving

Q.—*What is the treatment for dermatitis of the scalp caused by cold permanent waving?*

A.—If not due to idiosyncrasy, this is probably a chemical alkaline dermatitis. It may be necessary to cut the hair if there is much exudate and matting. A 0.5% aluminium acetate lotion, or washing the scalp with permanganate of potash 1 in 8,000 followed by the application of liquid paraffin or olive oil, would be suitable. An ointment composed of gentian violet 2½ gr. (0.16 g.), salicylic acid 5 gr. (0.32 g.), coconut oil 120 gr. (8 g.), Halden's emulsifying base 120 gr., with soft paraffin up to 1 oz. (31 g.), is also effective, the head being wrapped in a turban after the ointment has been applied, although the staining may not be appreciated.

The questioner might be interested in an article by Cohen (*Arch. Derm. Syph., Chicago,* July, 1949, p. 14).

Stilboestrol for Prostatic Cancer

Q.—*What is the scheme of dosage of stilboestrol for prostatic cancer, and how long can treatment be continued?*

A.—For cancer of the prostate it is usual to start with a dose of 5 mg. of stilboestrol daily. This is continued for one week, and the dose is then reduced to 0.5 or 1 mg. daily. The amounts given depend on the fall in the acid phosphatase level in the serum, which should be estimated at intervals, and on the response of symptoms, such as the relief of pain. There is therefore no fixed maintenance dose. This treatment can be continued indefinitely, and patients have been treated for several years.

Ozone as an Aerial Disinfectant

Q.—*A machine producing ozone is being installed to improve the stuffy atmosphere of a workroom. Is the prolonged inhalation of even small amounts of ozone harmful?*

A.—The action of ozone on the tissues is similar to that of chlorine: it irritates the mucous membranes, particularly the respiratory and ocular membranes. The *Heating, Ventilating and Air Conditioning Guide*, 1946, states that "the allowable concentrations in the breathing zone are very small, between 0.01 and 0.05 part per million parts of air. These are much

too small to influence bacteria. Higher concentrations are associated with a pungent, unpleasant odour and considerable discomfort to the occupants. One part per million causes respiratory discomfort, headaches, depression, and a lowering of the metabolic rate. . . ." Experimental evidence on the merits of ozone as an aerial disinfectant has led to the conclusion that ozone in concentrations that can be breathed over long periods without irritation cannot be expected to provide any effective protection against airborne bacterial infection. Perhaps the best way to improve a "stuffy atmosphere" in a workroom is by attention to ventilation.

Food Value of Glycerin

Q.—*Has glycerin any food value and does it conduce to putting on weight? I have used jam and marmalade made with glycerin instead of sugar for diabetic patients, as it has little carbohydrate value.*

A.—Glycerin is a trihydroxy-alcohol. It is absorbed readily, and after absorption acts as a source of energy. It is alleged that it lessens glycosuria in diabetics. As a food it spares fats but does not influence protein metabolism.

Fat Deposits

Q.—*A woman has large pads of fat over each hip-joint and the inner aspect of both knees; the swellings in the latter site are discoloured, somewhat inflamed, and a little painful. The upper part of her body, arms, face, neck, and breasts are normal. The patient suffered considerable privation as a Japanese P.O.W. and had beriberi. Treatment by diet, radiant heat, medicines, and glandular products has had little effect. Would this be a case of Dercum's disease, and can you suggest any treatment?*

A.—This description is not typical of Dercum's disease, in which the fat deposits are strikingly tender. It is somewhat more suggestive of symmetrical lipomatosis. However, in both conditions treatment is most unsatisfactory, and the patient in question appears to have tried almost all known therapeutic methods without benefit. As the deposits are so localized, it would be worth her while to consult a plastic surgeon, as possibly excision could be undertaken.

Kaolin and Bismuth

Q.—*During the war, in the treatment of gastric and intestinal conditions, bismuth compounds were largely replaced by substitutes that were more accessible or less costly. Now, although bismuth is readily obtainable, there appears to be a tendency to continue to prescribe the substitutes. Is there any authoritative evidence that salts of bismuth have a superior therapeutic value?*

A.—During the war bismuth compounds were replaced by kaolin. This is a fine powder, like bismuth carbonate, which acts by adsorbing irritant substances. Neither bismuth carbonate nor kaolin has much power to neutralize hydrochloric acid. There is no evidence that bismuth salts have a superior therapeutic value.

Barley Sugar and Cerebral Metabolism

Q.—*I have an elderly male patient suffering from a moderate degree of Parkinsonism. He finds that barley sugar gives him more direct benefit than any of the new drugs on the market. I note that Quastel states that the brain only absorbs nourishment in the form of glucose. Does this mean that table sugar and many forms of confections consisting of sucrose are of no therapeutic value?*

A.—Barley sugar is a vitrified form of sucrose. If the patient derives benefit from its use, therefore, it seems unnecessary to resort to glucose or to foods containing it. While Quastel would agree that glucose, which may be derived with fructose from the hydrolysis of sucrose, is the most plentiful metabolite supplied by the blood stream to the brain, he would hardly support the view that it is the brain's sole source of nourishment. He has himself shown that the brain may metabolize other substances, including glutamic acid.

NOTES AND COMMENTS

Transitory Retrobulbar Neuritis.—Dr. HUGH GARLAND (Leeds) writes: Your feature "Any Questions?" is often useful in supplying the answer to problems the answer to which might otherwise be difficult of access. The quality of the answers is usually high, but I would call your attention to the answer to the question, "What may be the cause, apart from disseminated sclerosis, of a transitory attack of retrobulbar neuritis?" (August 13, p 397). Your anonymous authority prefaces his answer by dividing the causes into three groups, of which the first is "functional disease." One can only assume that by this he refers to hysteria, but, if so, why not say so? He then states that various authors differ in their views about the place of nasal disease and focal sepsis as causes of transitory retrobulbar neuritis without making any critical comment of his own. Surely there is no shred of evidence that retrobulbar neuritis ever results from such localized sepsis. He goes on to state that there is a natural tendency to spontaneous recovery, but the question only relates to transitory attacks. He then proceeds to give a list of causes (presumably which he himself accepts) of the most remarkable diversity. Has anybody ever seen transitory amblyopia caused by alcohol, tobacco, or diabetes? The optic atrophy, enlarging scotomata, and progressive visual failure sometimes complicating pernicious anaemia are by no stretch of imagination transitory, and even with intensive liver treatment improvement is extremely slow. Is there any proof that either syphilis (and, if so, syphilis of what structure?) or plumbism ever causes transitory blindness? Why should post-partum as opposed to any other form of haemorrhage be singled out as a cause of this condition? His next cause is one of classic simplicity, "sepsis." Disturbances of nutrition as a cause of failing vision is presumably a reference to that form of optic atrophy seen not infrequently among prisoners-of-war, but there is nothing transitory about this condition, and so far as I know all the affected persons were left with permanent disorders of vision. In what way, one might ask, can menstrual disorders cause transient amblyopia, unless this be hysterical? And the same would apply to pregnancy.

One by no means uncommon cause of transient monocular blindness which is not mentioned is the aura of an attack of migraine. You might say that here the basis of the visual defect is not "retrobulbar neuritis," but I would suggest that if most of the above causes ever, in fact, operate they certainly do not produce an inflammatory lesion of the optic nerve. The final statement is that "some attempt has been made in this list to indicate the frequency of the causes," but I can find no reference to the frequency either of a single cause or of the condition itself. Surely it is time for the universal recognition of the fact that transient "retrobulbar neuritis" should always be regarded as a manifestation of disseminated sclerosis or one of the rarer demyelinating diseases of the central nervous system.

Acroparaesthesia.—Dr. M. G. GOOD (London, N.W.11) writes: With regard to the question on acroparaesthesia (*Journal*, August 27, p. 495), I should like to say that my personal experiences do not agree with the opinion expressed in textbooks on the nature of this disease, which in recent years seems to have become more frequent. In the last five years or so I have successfully treated more than a dozen cases, mostly in women, rarely in males. In my experience acroparaesthesia is caused by an "idiopathic myalgia" of the elbow. The characteristic "myalgic spots" are regularly to be found in the origin of the flexors and/or extensors of arm and wrist. An appropriate treatment with small quantities of procaine relieves the complaints and cures the disease without delay.

Angioneurotic Oedema.—Dr. S. H. CRAIG (Feeny, Co. Londonderry) writes: With reference to the question and answer under this heading ("Any Questions?" August 20, p. 448), I have suffered from this trouble for 30 years. I had very severe attacks, but I found that sodium citrate 1 dr. (4 g.) in water, increasing the dose by 1 dr. with every attack until I got up to 4 dr. (16 g.), acted like magic and never once failed. The attacks have been getting less frequent and are now only a few times a year.

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